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# SYNTHETIC METHODS BASED ON TELLURIUM AND FREE RADICAL CHEMISTRY

by

PIERRE L. BEAULIEU

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

Department of Chemistry

EDMONTON, ALBERTA
Spring, 1984

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D. L. J. Clive

Supervisor

RHMitchell

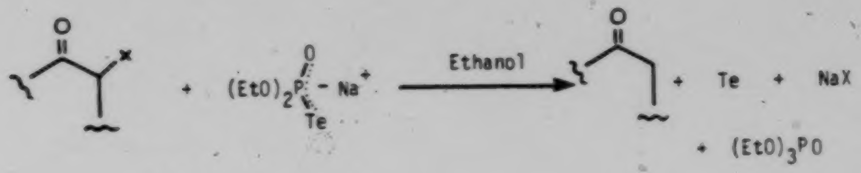
External Examiner

Date December 13 1983

TO MY FAMILY AND LORI

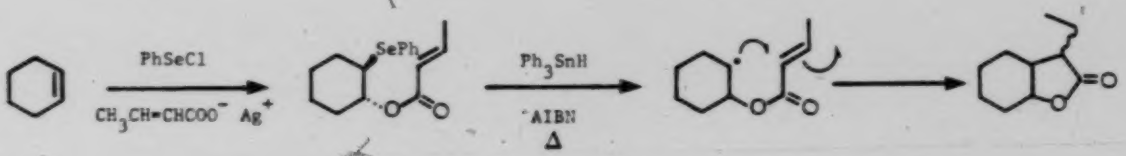
# ABSTRACT

This thesis consists of two parts. The first chapter describes the use of sodium *O,O*-diethyl phosphorotelluroate for the reductive dehalogenation of $\alpha$-haloketones:

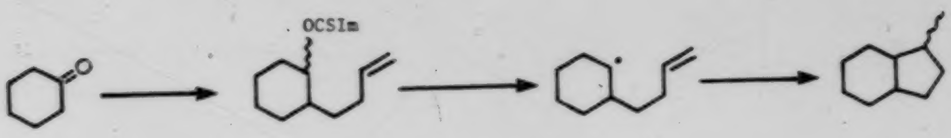


This new reaction complements other synthetic methods that perform similar conversions. In addition, the experiments provide an example of the use of a tellurium reagent to accomplish an organic transformation.

The second part of the thesis describes our work on intramolecular radical cyclizations. A new procedure for the formation of $\gamma$-lactones was invented. It involves the ionic addition of the elements of "PhSe" and "OCOCH=CHCH$_3$" across a double bond, and homolysis of the carbon–selenium bond with tin radicals. Intramolecular closure takes place in a regiospecific *exo*-manner leading to five-membered lactones:

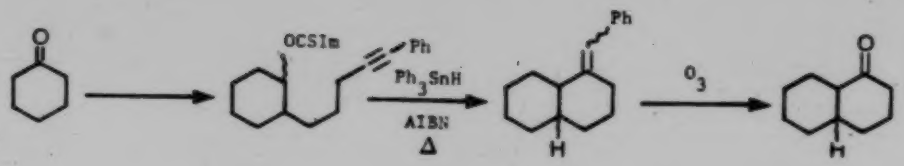


This reaction was developed further into a new method for the formation of carbocycles. The method was tested first with olefinic substrates and a hydroxyl group was used as a radical precursor via conversion to alkoxythiocarbonylimidazole esters:

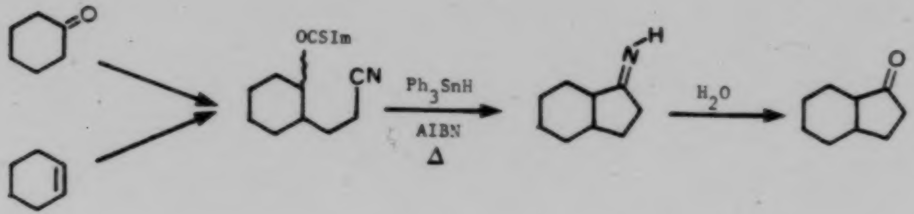


Im = N- Imidazoyl

A synthetically more useful version of this methodology involves acetylenic starting materials because further manipulation of the final product is then possible:


OCSIm
Ph
Ph$_3$SnH
AIBN
Δ
Ph
H
O$_3$
H

Finally, a new method for the preparation of substituted cyclopentanones was discovered and is based on $\delta$-cyano radicals.


OCSIm
CN
Ph$_3$SnH
AIBN
Δ
N
H
H$_2$O

All intramolecular radical cyclizations described in this work occurred regiospecifically in the *exo*– fashion giving rise to the smaller of the two possible ring sizes. The reactions also exhibited varying degrees of stereoselectivity that were most pronounced in the case of $\delta$-cyano radicals.

# ACKNOWLEDGEMENTS

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# CHAPTER 1

## REDUCTIVE DEHALOGENATION OF $\alpha$–HALOKETONES. USE OF SODIUM *O,O*–DIETHYL PHOSPHOROTELLUROATE

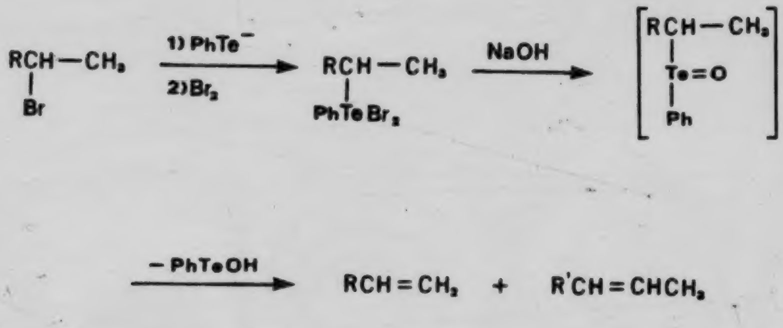
# I. INTRODUCTION

## GENERAL SURVEY OF APPLICATIONS OF TELLURIUM COMPOUNDS IN ORGANIC SYNTHESIS

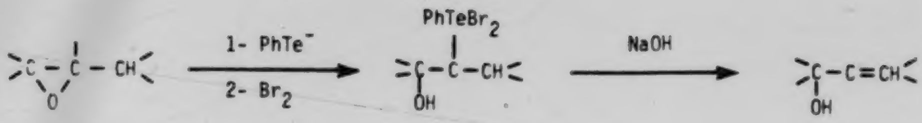
Unlike selenium, tellurium has found very little use as a reagent in organic synthesis. Until recently, most of the research had concentrated on means of introducing the element into organic molecules,[1] but, in the last few years there has been an increasing interest in the chemistry of this chalcogen and numerous publications are now unfolding its interesting properties.

### A. Telluroxide fragmentation

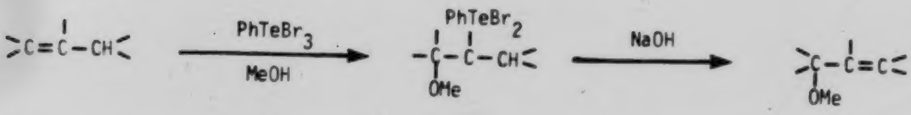
One of the most consequential aspects of selenium chemistry has been the discovery of the selenoxide fragmentation leading to carbon–carbon double bond formation.[2] In contrast, little is known about the telluroxide fragmentation. Early reports from Sharpless[3] and Cava[4] indicated that the reaction was rather limited in scope. It has now been demonstrated that the telluroxide fragmentation may be a useful synthetic method that can lead to the formation of olefins, allylic alcohols, and/or allylic ethers[5] (equ 1, 2, 3).



(equ. 1).

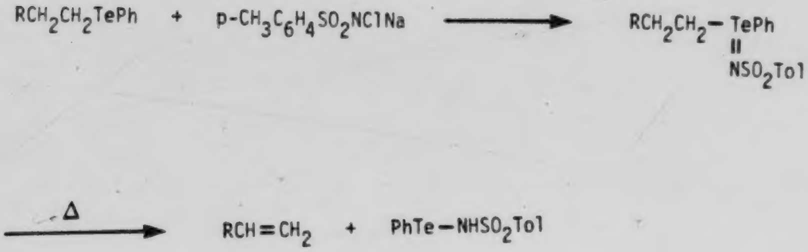


(equ 2)



(equ 3)

Relative to the analogous selenoxide and sulfoxide fragmentations the reaction shows a greater preference for elimination towards the less substituted carbon. n–Alkyl– and cyclohexyl telluroxides proved to be more resistant but could be made to undergo the desired elimination by pyrolysis without solvent at temperatures ranging from 200 to 240°C (yields were 50 to 72%). Another synthesis of olefins takes advantage of the thermal instability of tellurium sulfonimides generated from alkyl tellurides and chloramine–T[6] (equ. 4).



$$RCH_2CH_2TePh + p\text{-}CH_3C_6H_4SO_2NClNa \longrightarrow RCH_2CH_2\text{-}\underset{NSO_2Tol}{\overset{}{TePh}}$$

(equ. 4)

$$\xrightarrow{\Delta} RCH{=}CH_2 + PhTe\text{-}NHSO_2Tol$$

### B. Reductions and dehalogenations with $H_2Te$ and NaHTe

The properties of hydrogen telluride, $H_2Te$, and its sodium salt, NaHTe, have been extensively studied. Both exhibit unique reducing characteristics. Aldehydes and ketones can be reduced to the corresponding alcohols with hydrogen telluride, generated *in situ* from aluminum telluride and water[7] (equ. 5), while nitroaryls give aromatic amines[8] (equ. 6).

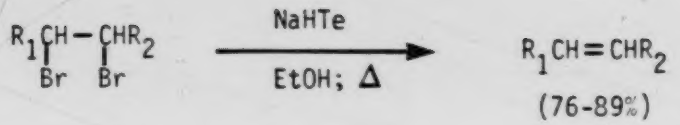
$$\mathrm{PhCHO} \xrightarrow[H_2O]{Al_2Te_3} \mathrm{PhCH_2OH} + 2\ \mathrm{Al(OH)_3} + 3\ \mathrm{Te} \qquad \text{(equ 5)}$$

$$\mathrm{Aryl-NO_2} \xrightarrow[H_2O]{Al_2Te_3} \mathrm{Aryl-NH_2} + 2\ \mathrm{Al(OH)_3} + 3\ \mathrm{Te} \qquad \text{(equ 6)}$$

$\alpha,\beta$–Unsaturated carbonyl compounds are reduced exclusively in a 1,4–fashion by hydrogen telluride[7] and by its sodium salt generated *in situ* from elemental tellurium and sodium borohydride[9] (equ. 7).

$$\mathrm{Ar-CH{=}CH-CHO} \xrightarrow[\substack{\text{or} \\ Al_2Te_3\ /\ H_2O}]{\substack{Te\ /\ NaBH_4 \\ \text{Ethanol}}} \mathrm{Ar-CH_2CH_2CHO} \qquad \text{(equ 7)}$$

Sodium hydrogen telluride has also proven to be efficient for dehalogenation of *vic*–dibromoalkanes to alkenes[10] (equ. 8).



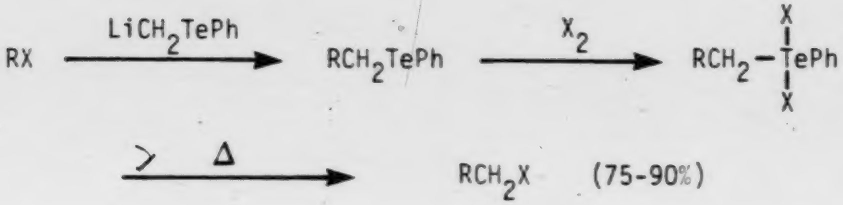
$$R_1\underset{Br}{CH}-\underset{Br}{CHR_2} \xrightarrow[EtOH;\ \Delta]{NaHTe} R_1CH{=}CHR_2 \quad (76\text{-}89\%)$$

(equ 8)

The same transformation can be achieved with diaryl tellurides,[11] diarylditellurides[12] and lithio 2–thiophenetelluroates[13]

## C. Formation of carbon–carbon bonds

Halogenation of alkyl tellurides to tellurium (IV) species and pyrolysis gives alkyl halides. This reaction offers possibilities for carbon chain extension[14] (equ 9)



$$RX \xrightarrow{LiCH_2TePh} RCH_2TePh \xrightarrow{X_2} RCH_2-\overset{X}{\underset{X}{Te}}Ph \xrightarrow{>\ \Delta} RCH_2X \quad (75\text{-}90\%)$$

(equ 9)

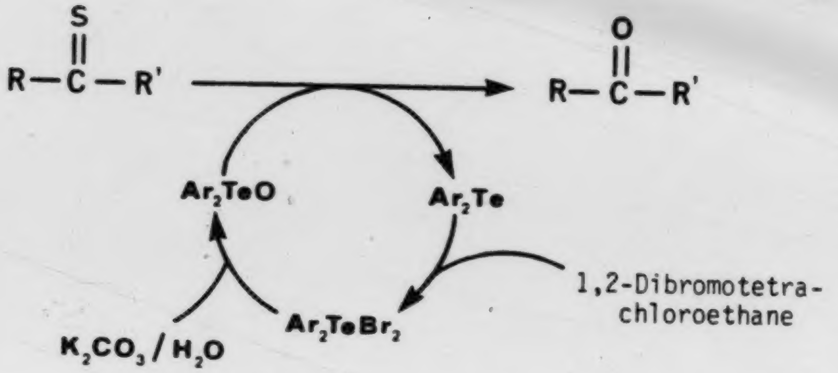
A similar sequence with bis–(phenyltelluro)methyllithium can lead to aldehydes[14] (equ 10)

$$RX \xrightarrow{LiCH(TePh)_2} RCH-(TePh)_2 \xrightarrow[NaI,\ H_2O]{I_2} RCHO \quad (77\text{-}93\%)$$

(equ 10)

### D. Telluroxides as oxidizing agents

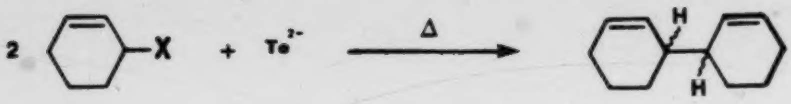
Diaryl telluroxides have been used as mild and selective oxidizing agents.[15] Thiocarbonyl derivatives are converted into their oxo— analogues and disulfides are formed from thiols. The reagent is also effective for the oxidation of hydroquinones to quinones, acyl hydrazines to diacyl hydrazines, and phosphines to phosphine oxides. The oxidation of thiocarbonyl species to their oxo counterpart can be made catalytic in the tellurium reagent by use of a halogenating agent[16] (equ. 11).



(equ. 11)

### E. Miscellaneous

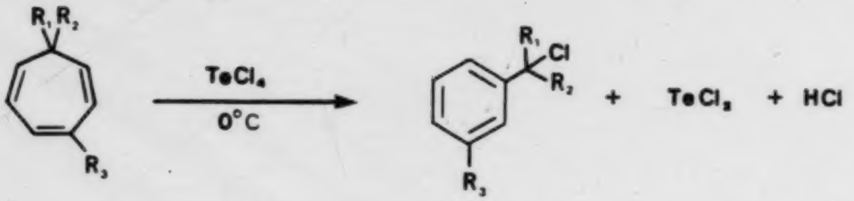
Other uses of tellurium in synthetic methodology include the coupling of allylic halides with Te$^{2-}$ to afford 1, 5—dienes[17] (equ. 12), the tellurium catalyzed carbonylation of amines with carbon monoxide to produce urea derivatives[18] (equ. 13), and the rearrangement of various cycloheptatrienes to benzene derivatives involving the use of tellurium tetrachloride as reagent[19] (equ. 14).



(equ. 12)

$$2\ RNH_2 + CO \xrightarrow{Te} \underset{\text{(ca. 30\%)}}{(RNH)_2CO} + Te + RNHCHO$$

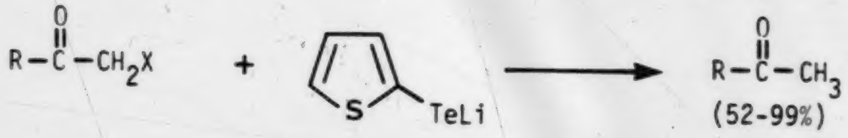
(equ. 13)



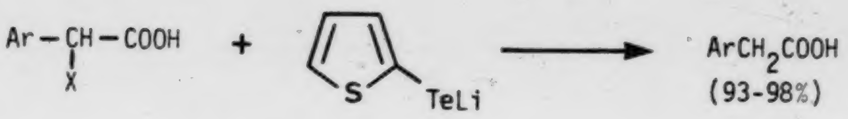
(equ 14)

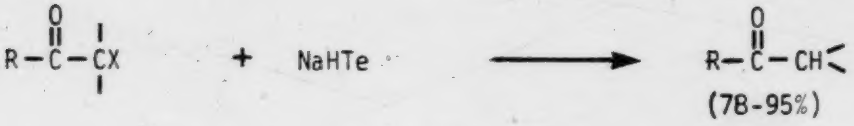
F. **Reductive dehalogenation of $\alpha$–halocarbonyl compounds**

There are two reports in the literature invoking the use of tellurium reagents for the reductive dehalogenation of $\alpha$–halocarbonyl compounds. Lithium and sodium 2–thiophenetellurolates convert $\alpha$–haloketones and acids into the corresponding halogen–free products. Acetoxy, mesyloxy and phenylthio groups are also removed[20] (equ. 15, 16). More recently, sodium hydrogen telluride was found to perform the same transformation[21] (equ. 17).

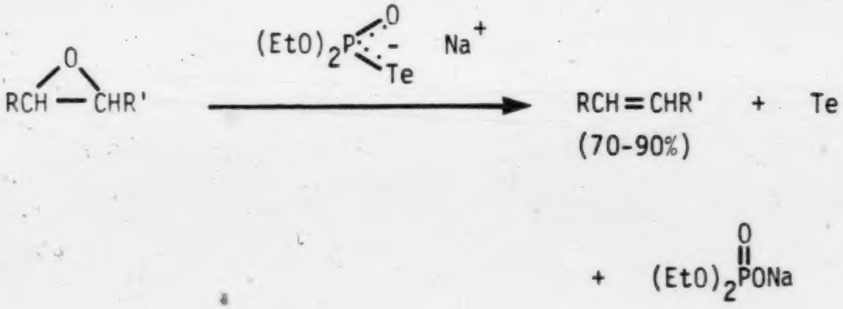


(equ. 15)


(equ. 16)


(equ. 17)

In 1977, Clive[22] reported that alkali metal *O,O*–diethyl phosphorotelluroates are mild reagents for deoxygenating epoxides (equ. 18). This was probably the first example of a tellurium reagent that could be used for a transformation that was not easy by classical methods.


(equ. 18)

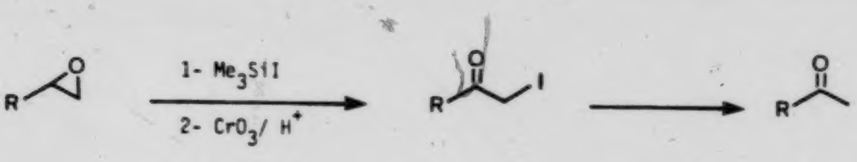
The reagent was generated *in situ* in ethanol from elemental tellurium and sodium diethyl phosphite. The deoxygenation was stereospecific and could be made catalytic in tellurium.

The above summary, equ. 1 – 18, represents the synthetic transformations that can be brought about with tellurium reagents. Clearly, the subject is not nearly as well–developed as selenium chemistry and much further research is required in order to establish the relevance of tellurium compounds to organic synthesis

# II. RESULTS AND DISCUSSION

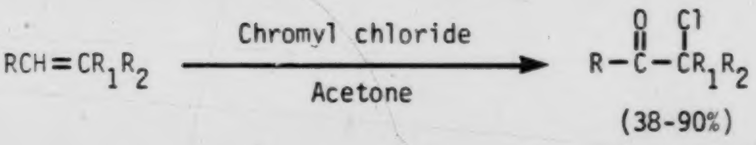
## A. Introduction

The removal of a halogen atom from an $\alpha$–haloketone is a transformation that is sometimes used in organic synthesis. For example, epoxides can be converted to ketones via their $\alpha$–iodinated derivatives[23] (equ. 19)



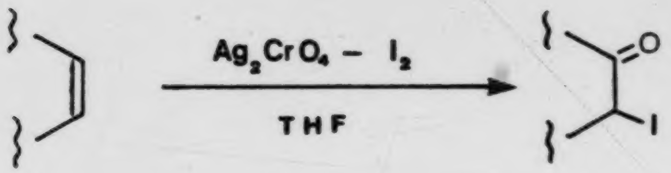
(equ. 19)

Alkenes react with chromyl chloride[24] or silver chromate–iodine to give $\alpha$–haloketones[25] (equ. 20, 21), that are potential precursors to ketones.



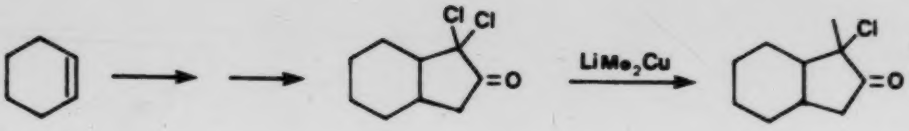
$$RCH{=}CR_1R_2 \xrightarrow[\text{Acetone}]{\text{Chromyl chloride}} R-\overset{\overset{\large O}{\|}}{C}-\overset{\overset{\large Cl}{|}}{C}R_1R_2 \quad (38\text{-}90\%)$$

(equ. 20)



(equ. 21)

Easily accessible $\alpha,\alpha$–dichlorocyclopentanes allow monoalkylation of a five membered ring ketone, a task that can often prove problematic[25] (equ. 22).



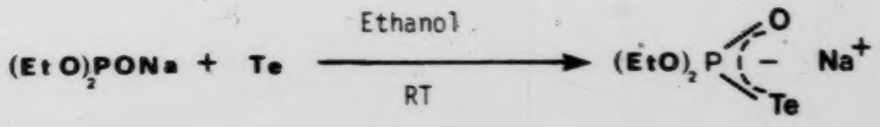
(equ. 22)

As the above reactions (equ. 19–22) indicate, dehalogenation of $\alpha$–haloketones can serve to generate the parent ketone.[26]

In the last decade a number of reagents have been introduced for this purpose. Many of the procedures, however, suffer from lack of selectivity or low yields. Zinc in acetic acid,[27] tin hydrides,[28] trimethylsilyl iodide[29] and sodium borohydride–metal ions[30] are not selective reagents and can alter many other functionalities, thus limiting their utility. Molybdenum hexacarbonyl,[31] iron pentacarbonyl,[32] and diphenyl phosphine[33] are toxic and expensive. Triphenylphosphine fails to perform the transformation in many simple cases.[34] Iodide ions are ineffective in hindered situations[35] unless a Lewis acid is present to facilitate nucleophilic attack.[36] Tertiary amine–$SO_3$ complexes will not dehalogenate $\alpha$–halocycloalkanones unless pyridine–$SO_3$ is used under more drastic conditions.[37] Transition metal ions such as vanadium (II) chloride[38] and titanium (III) chloride[39] have been used quite successfully, whereas pyridine–sodium dithionite[40] and *N,N*–dimethylaniline[41] operate with varying yields. Most recently, two tellurium reagents, lithio 2–thiophenetellurolate[20] and sodium hydrogen telluride[21] have been shown to perform very satisfactorily and these reactions are indicative of a still growing interest in tellurium chemistry. Before the publication of the above tellurium reagents,[20], [21] we had been looking for other uses for the easily accessible *O,O*–diethyl phosphorotelluroates and had found that they would induce reductive dehalogenation of $\alpha$–chloro– and $\alpha$–bromoketones.[42] The first chapter of this thesis describes our results on this new reaction.

## B. Results

Until the discovery that they could deoxygenate epoxides under very mild conditions,[22] little was known of alkali metal *O,O*–diethyl phosphorotelluroates. The potassium salt was reported in 1950[43] but its synthetic potential was not explored. Furthermore, it was observed to be unstable in air, depositing elemental tellurium when exposed. Sodium *O,O*–diethyl phosphorotelluroate **1** is easily prepared by dissolving finely divided tellurium metal in an ethanolic solution of sodium diethyl phosphite as shown in equation 23.



1

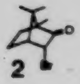
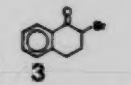
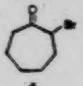
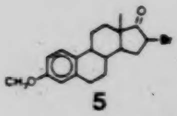
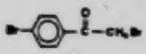
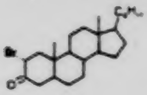
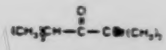
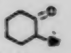
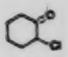
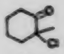
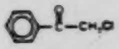
(equ 23)

The colorless solution of the reagent can be used directly or the salt can be isolated by evaporation of the solvent under vacuum. These solutions are very air–sensitive and must be handled under an inert atmosphere. Precipitated tellurium was used in the preparation of **1** to ensure rapid and complete reaction with sodium diethyl phosphite. Powdered tellurium was found to be much less reactive, and required long periods of stirring before dissolution was complete. The reagent has been assigned structure **1** on the basis of its chemical behavior and NMR characteristics.[22]

When an ethanolic solution of 2,4'–dibromoacetophenone, **6**, (see Table 1), (1 equivalent) was injected into a solution of **1** (1 equivalent) an orange coloration first appeared (indicative of the formation of a telluride), rapidly followed by a black precipitate of finely divided tellurium. From the reaction mixture *p*–bromoacetophenone was isolated in 78% yield. When the experiment was repeated with other $\alpha$–haloketones, similar results were obtained. These experiments are sumarized in Table 1.

The identity of the products was established firmly by comparison with authentic samples (TLC, VPC, $^1$H NMR). $\alpha$–Halocycloalkanones proved to be more resistant, but dehalogenation occurred when the reaction was conducted at 80°C. Bromides were more reactive than chlorides as revealed by entries 8 and 9: 2–bromocyclohexanone gave a 56% yield of cyclohexanone after two hours at 80°C whereas a 36% yield of the ketone was obtained from 2–chlorocyclohexanone after seven hours at the same temperature. An increase in substitution at the halogen site also decreases the yield and reactivity. This is exemplified by entries 9 and 10, and is indicative of a mechanism involving bimolecular nucleophilic substitution at some stage of the reaction. Hindered substrates such as 3–

## TABLE 1
## REDUCTIVE DEHALOGENATION OF α-HALOKETONES

| ENTRIES | SUBSTRATES[a] | TEMP °C | TIME h | YIELDS[b] (%) |
|---|---|---|---|---|
| 1 |  **2** | 80 | 5.0 | 79 |
| 2 |  **3** | 25 | 3.0 | 91 |
| 3 |  **4** | 25 | 3.5 | 89[c] |
| 4 |  **5** | 25 | 0.75 | 96 |
| 5 |  **6** | 25<br>60 | 2.5<br>0.25 | 78<br>78 |
| 6 |  **7** | 25 | 4.0 | 81 |
| 7 |  $(CH_3)_2CH-\overset{O}{\overset{\Vert}{C}}-CBr(CH_3)_2$ **8** | 80 | 3.5 | 48[c] |
| 8 |  **9** | 80 | 2.0 | 56[c] |
| 9 |  **10** | 80 | 7.0 | 36[c] |
| 10 |  **11** | 80 | 15.0 | 19[c] |
| 11 |  **12** | 25 | 1.0 | 84 |

[a] Experiments were run on a 1 mmol scale except for entries 4 and 6 which were on a 0.125 mmol scale. A stoichiometric amount of tellurium and a 20% excess of sodium diethyl phosphite was used in all cases. Ethanol was the solvent except for entries 1, 4, 5 and 6 where ethanol–THF was used.

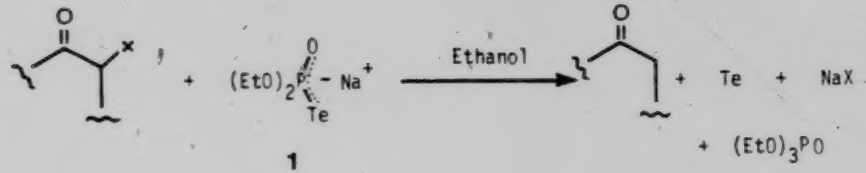
[b] Yields refer to pure isolated material, except where indicated.

[c] Yield determined by VPC using an internal standard.

bromocamphor **2** and 2$\alpha$–bromocholestan–3–one **7** underwent reductive dehalogenation in good yield.

## C. Discussion

The stoichiometry of the reaction is depicted in equation 24.



**1** **13**

(equ 24)

Tellurium metal is regenerated in the process and this means that only a catalytic amount of the element is required for the reaction to proceed. This fact was verified in experiments with 2–bromocycloheptanone **4** as shown in Table 2 (p. 15).

One sees that a full equivalent of tellurium is not required, but for best results, a stoichiometric amount ensures a good yield and a short reaction time.

Triethyl phosphate, **13**, was also detected as one of the reaction products. It was identified by VPC (*ca.* 100% yield) and $^1$H NMR in an experiment with 2,4′–dibromoacetophenone, **6**. Bromoethane could not be detected (VPC) at any stage of the reaction indicating that halide attack on one of the ethoxy groups attached to phosphorus does not occur. A reasonable mechanism that accounts for these observations is shown in Scheme 1 (p. 16). The first step is an $S_N2$ displacement of halide ion from the $\alpha$–haloketone by reagent **1** giving rise to ester **14**. Analogy for the intermediacy of **14** is provided by the observation that the selenium salt, **16**,[44] corresponding to **1** reacted with 2,4′–dibromoacetophenone **6**, to give a similar selenophosphate ester **17**, as shown in equation 25.

Under conditions that yielded smooth reductive dehalogenation with the tellurium

## TABLE 2
## DEHALOGENATION OF 2-BROMOCYCLOHEPTANONE USING *O,O*-DIETHYL PHOSPHOROTELLUROATE

| **4** (mmol) | Sodium diethyl phosphite (mmol) | Tellurium (mmol) | Temp °C | Time (h) | Yield[a] % |
|---|---|---|---|---|---|
| 1.0 | 1.2 | 1.0 | 25 | 3.5 | 89 |
| 1.0 | 1.2 | 0.67 | 25 | 15.0 | 86 |
| 1.0 | 1.2 | 0.14 | 25 | 5.0 | 67 |

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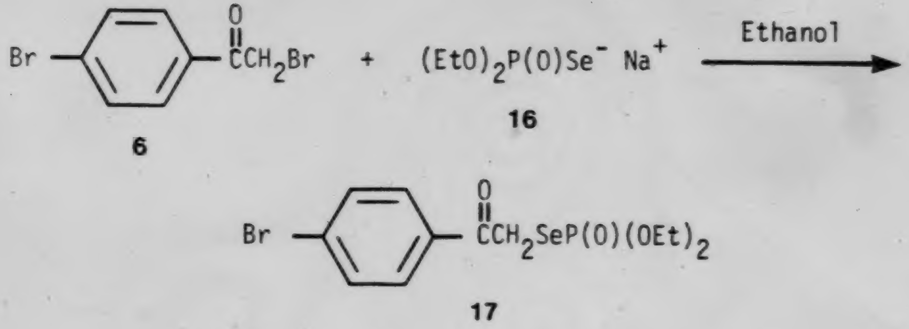
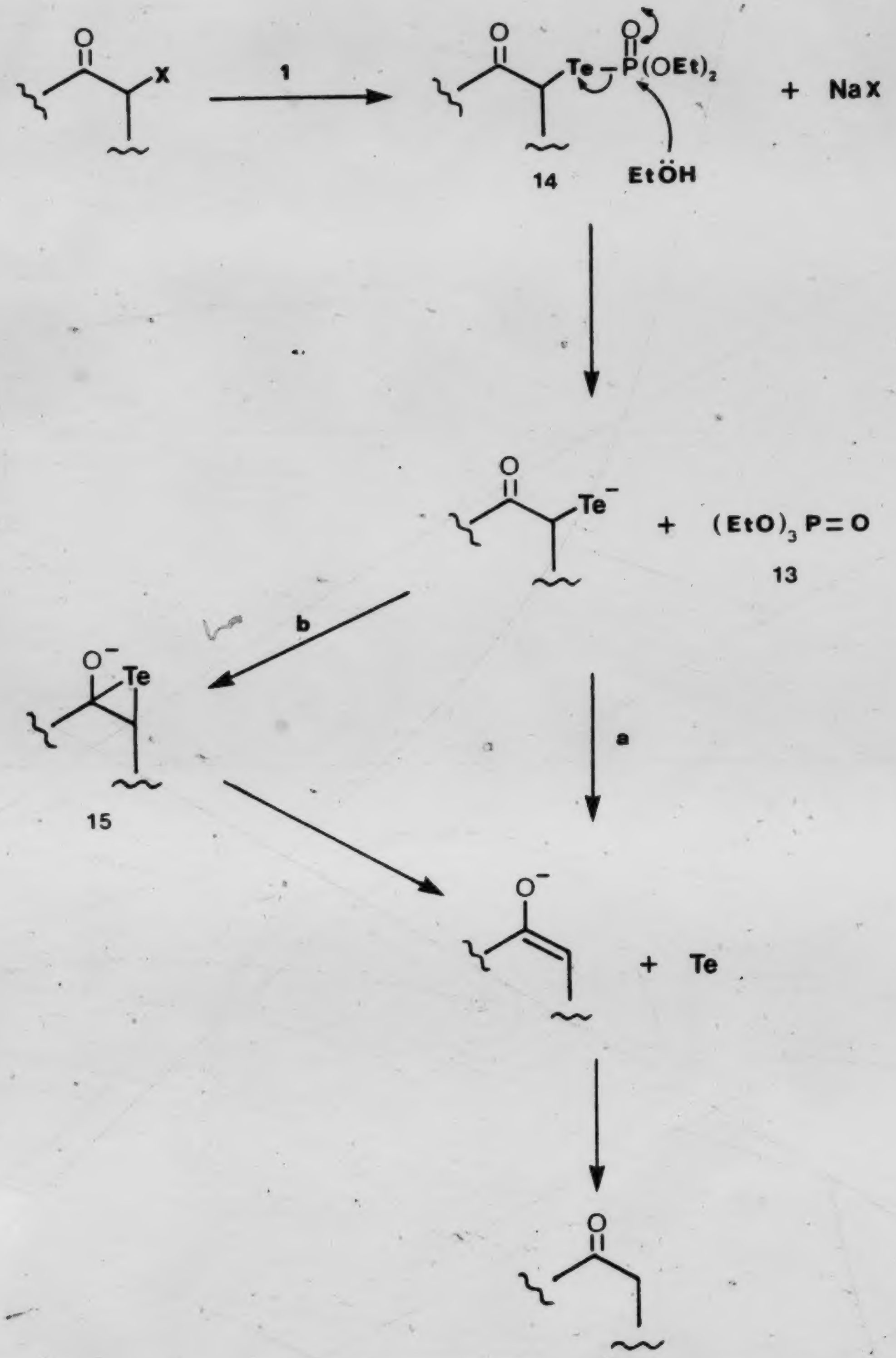
[a] Yields were determined by VPC analysis using an internal standard.

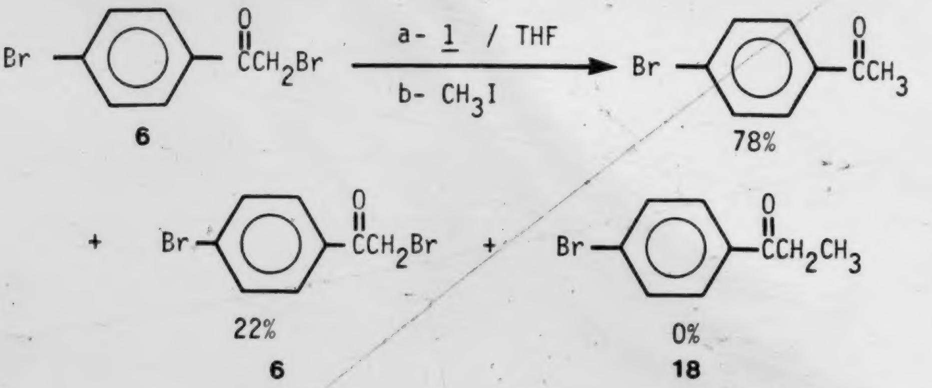

Br
O
CCH2Br
+
(EtO)2P(O)Se⁻ Na⁺
Ethanol
6
16
Br
O
CCH2SeP(O)(OEt)2
17

(equ. 25)

Scheme 1


X
1
Te – P(OEt)₂
+ NaX
14
EtÖH
Te⁻
+ (EtO)₃P=O
13
b
a
Te
15
+ Te

reagent, ester **17** did not react further and could be isolated for characterization. Most diagnostic for that purpose were the NMR spectra which showed a singlet in the $^1H$ NMR spectrum at 4.19 ppm for $CH_2-SeP(O)(OEt)_2$ and a 7–peak multiplet in the $^{31}P$ spectrum at 18.6 ppm downfield from $H_3PO_4$ with an extra $J_{Se-P}$ coupling of 450 Hz. These values are in good agreement with the presence of a selenophosphate ester. For example $(EtO)_2P(O)SeCH_3$ has a $^{31}P$ resonance at 18.5 ppm downfield from 85% $H_3PO_4$.[22] Also characteristic of ester **17** was an IR (P=0) absorption at 1587cm$^{-1}$ and a molecular ion at m/e 413.9135 in the mass spectrum consistent with the molecular formula $C_{12}H_{16}BrO_4PSe$. The next step in Scheme 1 is a nucleophilic attack of the solvent, ethanol, on the phosphorus atom. Triethyl phosphate is thus generated at this stage and the telluride ion breaks down to the enolate form of the dehalogenated ketone. This can occur directly (path a) or via epitelluride **15** (path b). The facile extrusion of tellurium metal from epitellurides has been documented.[45] Protonation of the enolate by the solvent occurs at any stage after elimination of triethyl phosphate from ester **14**. In order to further substantiate the proposed mechanism, attempts were made to trap the postulated enolate by alkylation with iodomethane. In order to achieve this, it was necessary to perform the reaction in an aprotic solvent to prevent direct protonation of the enolate. To this end, salt **1** was isolated from its ethanolic solution and the reaction with 2,4′–dibromoacetophenone **6**, was carried out in THF. After 16 hours at room temperature, p–bromoacetophenone and starting material **6**, were obtained in a 3.6:1 ratio. This large decrease in reactivity (the usual time in ethanol is 2.5 hours for complete reaction) is consistent with the involvement of an external nucleophile (usually solvent ethanol) in the breakdown of telluroester **14**. In two further experiments performed in THF, iodomethane was added to the reaction mixture 5 minutes and 3.5 hours, respectively, after mixing. However, no p–bromopropiophenone **18**, was detected by $^1H$ NMR (equ. 26).

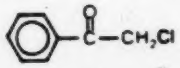
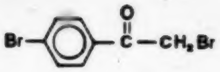


(equ. 26)

Of course, the mechanism of the reaction may not be the same in ethanol as in THF, but, in the event, alkylation attempts in THF did not serve to define the mechanism in the aprotic solvent.

In control experiments, it was found that sodium diethyl phosphite itself effects slow dehalogenation but the yields are poor. These observations are shown in Table 3. This result can be understood in terms of a difference in nucleophilicity between telluride 1 and sodium diethyl phosphite.

## TABLE 3
## DEHALOGENATION OF α-HALOKETONES USING *O,O*-DIETHYL PHOSPHOROTELLUROATE AND SODIUM DIETHYL PHOSPHITE

| HALOKETONE | REAGENT[a] | TEMP. (°C) | TIME (h) | YIELD[b] (%) |
|---|---|---|---|---|
|  12 | $(EtO)_2P(O)TeNa$ | 25 | 1 | 84 |
| | $(EtO)_2P(O)Na$ | 25 | 72 | 60 |
| | $(EtO)_2P(O)Na$ | 25 | 1 | 0 |
|  6 | $(EtO)_2P(O)TeNa$ | 25 | 2.5 | 78 |
| | $(EtO)_2P(O)Na$ | 25 | 24 | 18 |

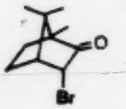
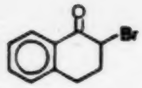
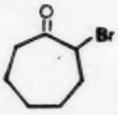
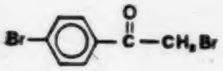
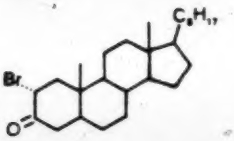
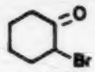
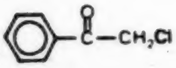
[a] Reactions run in ethanol–THF.

[b] Yield refers to isolated ketone.

## III. CONCLUSION

As mentioned previously several methods are available to bring about the reductive dehalogenation of $\alpha$–haloketones. The present method is a useful addition in view of the following characteristics: mild conditions, easy access to the reagent, simple experimental manipulation and low cost. The reagent that we have introduced is also one of broad versatility as it is compatible with many other functionalities. Table 4 is an explicit comparison of our tellurium reagent with other published methods. The yields are usually comparable and/or complimentary to the available methodology. Finally, sodium *O,O*–diethyl phosphorotelluroate represents a new contribution to the use of tellurium in organic synthesis.

## TABLE 4
## COMPARISON OF VARIOUS REAGENTS FOR REDUCTIVE DEHALOGENATION OF α-HALOETONES

| HALOKETONE | $(EtO)_2P(O)TeNa$ (%) | OTHER METHODS |
|---|---|---|
|  | 79 | 87[a]; 78 or 61[h]; 59[i];<br>85[j]; 78[f] |
|  | 91 | 56[d]; 96[f] |
|  | 89 | 88[a]; 72[e] |
|  | 78 | 72[b] 25[c]; 65[e]; 100[g];<br>66[i]; 98[j]; 93[f]; 72 or 98[K] |
|  | 81 | 96[j]; 90 or 93[l] |
|  | 36 | 78[a] |
|  | 84 | 91[a]; 57[d]; 55[e]; 100[g]; 84[h];<br>84[h]; 95[f]; 62 or 93[K] |

[a] $Me_3SiCl/NaI$: ref. 29.

[b] $Mo(CO)_6$: ref. 31.

[c] $Mo(CO)_6$: ref. 31.

[d] $Fe(CO)_5$: ref. 32.

[e] Pyridinium salt: ref. 40.

[f] NaHTe: ref. 21.

[g] $Ph_2PH$: ref. 33.

[h] $Bu_2SnH_2$ or $Bu_3SnH$: ref. 28.

[i] $HFe(CO)_4^-$: ref. 32.

[j] $LiI/BF_3$: ref. 36.

[k] Lithium-2-thiophenetellurolate: ref. 20.

# IV. EXPERIMENTAL

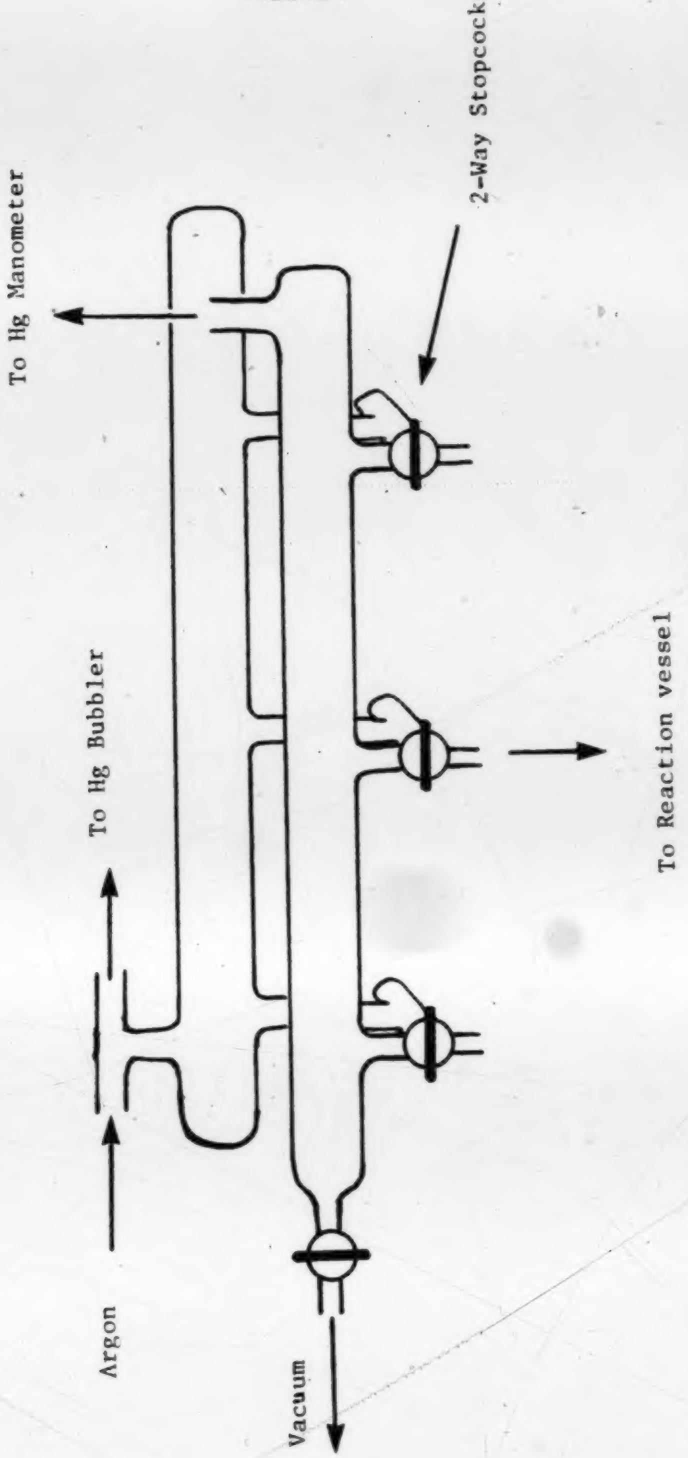
## A. General

Unless otherwise stated the following particulars apply. For reactions carried out under an inert atmosphere, the double line technique described below and oven–dried glassware were used. The apparatus shown in Figure 1 consists of a high vacuum line and an argon line. The latter is connected to a mercury bubbler to allow for the release of excess pressure. Alternate access to either the vacuum or the argon line is gained by means of two–way stopcocks. The line was connected to the hot (oven–dried) apparatus in which the reaction was to be performed by means of ground–glass joints or via a needle through a rubber septum. The system was alternately evacuated and flushed with argon three times and kept under a slight static pressure of the inert gas.

Syringes and syringe needles were oven–dried and allowed to cool in a desiccator. All solvents were distilled before use for chromatography. Where required, solvents and reagents were dried with suitable drying agents and distilled under argon. Dry ether, tetrahydrofuran (THF), and dioxane were distilled from sodium–benzophenone ketyl; dichloromethane, chloroform, carbon tetrachloride, 1, 2–dichloroethane, benzene, toluene, hexane, pyridine, triethylamine, diisopropylamine, 1, 3–diaminopropane, acetonitrile, dimethylsulfoxide, and hexamethylphosphoric triamide (HMPA) from calcium hydride [the latter two under reduced pressure (*ca.* 10 mm)]. Acetone was distilled from calcium sulfate (Drierite); methanol from magnesium methoxide; absolute ethanol was from a commercial source and was used without further purification; deuterated chloroform for NMR was stored over 4 A molecular sieves. Magnesium turnings for Grignard reactions were stored at 130°C. The commercial solutions (Aldrich) of methyllithium in ether and n–butyllithium in hexane were titrated before use by the diphenyl acetic acid method.[62] Benzeneselenenyl chloride (Aldrich) was used as received and stored in a desiccator. Azobisisobutyronitrile (AIBN) from Eastman was used without further purification and stored at 0°C.

Products were isolated from solution by concentration under water pump vacuum at 30°C using a rotary evaporator. Where compounds were isolated by simple evaporation of their solutions, the residues were kept under vacuum (<1.0 mm) until of

FIGURE 1


2-Way Stopcocks
To Hg Manometer
To Hg Bubbler
To Reaction vessel
Argon
Vacuum

constant weight. Stirring was done by means of a Teflon coated magnetic stirring bar unless otherwise stated. Vapor phase chromatography(VPC) analyses were performed on a Hewlett–Packard 5830A gas chromatograph equipped with an FID detector and prepacked Hewlett–Packard columns (6 ft) with nitrogen as carrier gas. Columns used were:

10% DEGS on chromosorb W, 80–100 mesh.
10% Apiezon L on chromosorb W, 80–100 mesh
10% carbowax 20M on chromosorb W, 80–100 mesh
10% FFAP on chromosrob W, 80–100 mesh
10% QF–1 on chromosorb W, 80–100 mesh

VPC yields were evaluated in the following way. Suppose compound A is to be prepared by a certain reaction and the yield is to be measured by using an internal standard B. A solution is prepared containing *a* g of authentic A and *b* g of B. After VPC analysis compound A gives a peak count $C_A$ and compound B gives a peak count $C_B$. The reaction is then carried out in the presence of *b'* g of standard B. *a'* is the theoretical yield of compound A. After VPC analysis of the reaction mixture, the peak due to A is $C'_A$ counts and that due to B is $C'_B$ counts. The VPC yield of A for the reaction is given by:

$$\%\ \text{YIELD} = \frac{ab'C'_AC_B}{a'bC_AC'_B} \times 100\%$$

Commercial silica (Merck 60F–254) thin–layer chromatography (TLC) plates were used. UV active spots were detected at 254 nm; spots were also revealed with iodine vapor and by charring after spraying with sulfuric acid (50% in methanol). Throughout the text, "normal" silica gel for column chromatography refers to Merck's type 60, 70–230 mesh ASTM; silica gel for flash chromatography[66] was Merck type 60, 230–400 mesh ASTM.

Spinning band distillations were carried out on a Perkin–Elmer 151 annular still. Melting points were determined on a Kofler block apparatus. Melting points and boiling points are uncorrected. Boiling points quoted for products distilled in a Kugelrohr apparatus refer to the oven temperature.

Combustion elemental analyses were performed in the microanalytical laboratories of the University of Alberta.

Infrared spectra were recorded on a Perkin–Elmer 297 infrared spectrophotometer; liquids were run as neat films on potassium chloride plates; solids were run as solutions in the specified solvent, using 0.5 mm potassium chloride cells.

Proton NMR spectra were recorded on Bruker WP–80 (at 80 MHz), Perkin–Elmer R32 (at 90 MHz), Varian HA–100 (at 100 MHz), Bruker WH–200 (at 200 MHz) or Bruker WH–400 (at 400 MHz) spectrometers, in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. $^{13}$C NMR spectra were recorded on Bruker HFX–90 (at 22.6 MHz), Bruker WH–200 (at 50.3MHz) or Bruker WH–400 (at 100.6 MHz) spectrometers in deuterated chloroform with tetramethylsilane as an internal standard. $^{31}$P NMR spectra were recorded on a Bruker HFX–90 (at 36.43 MHz) spectrometer in the specified solvent using 85% phosphoric acid as an external standard. The following abbreviations are used in the text: s, singlet; d, doublet; t, triplet; q, quartet; q', quintet; m, multiplet; J, coupling constant; $J_{1/2}$, coupling constant at half–height; $\delta$, chemical shift.

Mass spectra were recorded on an A.E.I. MS50 mass spectrometer at an ionizing voltage of 70 EV.

## B. Starting Materials

The following $\alpha$–haloketones were prepared by the methods described in the literature: (1*R*–*endo*)–3–Bromo–1,7, 7–trimethylbicyclo[2.2.1]heptan–2–one,[46] 2$\alpha$–bromocholestan–3–one,[47] 2–bromo–3, 4–dihydro–1– (2*H*)–naphthalenone,[48] 16$\alpha$–bromo–3–methoxyestra–1, 3, 5(10)–trien–17–one,[49,50] 2–chloro–2–methylcyclohexanone,[51] 2–bromocycloheptanone,[52] 2–chlorocyclohexanone,[53] 2–bromocyclohexanone,[54] and 2–bromo–2,4–dimethylpentan–3–one.[55] 2–Chloroacetophenone and 2,4'–dibromoacetophenone were commercial samples.

**Standard ethanolic solution of sodium diethyl phosphite:**[22] Sodium metal (1.30 g, 56.55 mmol) was placed in a dry 100–mL round–bottomed flask containing a Teflon–coated magnetic stirring bar and equipped with a reflux condenser fitted with a rubber septum. The system was purged with argon via a needle passing through the septum, and absolute ethanol (50.0 mL) was added by syringe to generate a solution of sodium ethoxide. The solution was cooled to room temperature and diethyl phosphite (Aldrich, 7.3 mL, 56.55 mmol) was injected. The resulting solution of sodium diethyl phosphite (*ca.* 1.0 M) was stirred at 25°C for an additional hour before use. Such solutions could be stored at ambient temperature under an argon atmosphere for a maximum of four weeks.

**Standard tetrahydrofuran solution of sodium diethyl phosphite:** Sodium metal (0.56 g, 24.35 mmol) was placed in a dry 100–mL round–bottomed flask containing a Teflon–coated magnetic stirring bar and equipped with a reflux condenser fitted with a rubber septum. The system was purged with argon via a needle passing through the septum and dry tetrahydrofuran (20.0 mL) was added (syringe) followed by diethyl phosphite (Aldrich, 3.14 mL, 24.35 mmol). The mixture was refluxed for 2 h at which stage hydrogen evolution had stopped (and all the sodium metal had dissolved). The resulting solution was 1.05 M in sodium diethyl phosphite and was used immediately. The storage life of such solutions was not measured.

**Precipitated tellurium metal:** In order to reduce the reaction time with sodium diethyl phosphite (in the preparation of ethanolic solutions of sodium *O,O*–diethyl phosphorotelluroate), it was found necessary to use precipitated tellurium metal of homogeneous particle size. This material was prepared by a literature procedure.[56]

**Sodium *O,O*–diethyl phosphoroselenoate.** This material was prepared as a white solid as described in the literature.[44]

### C. Dehalogenation of α-haloketones

**General procedure:** Finely precipitated tellurium (0.1280 g, 1.0 mmol) was placed in a 15–mL oven–dried flask containing a magnetic stirring bar and fitted with a rubber septum. For reactions done above room temperature, the flask was equipped with a reflux condenser. The system was purged with argon, a standard ethanolic solution of sodium diethyl phosphite (1.0 M, 1.5 mL, 1.5 mmol) was injected into the flask and the mixture was stirred (*ca.* 5 min) until a clear solution of sodium *O,O*–diethyl phosphorotelluroate had formed. The $\alpha$–haloketone (1.0 mmol) in dry ethanol or THF (1.5 mL plus a 0.5 mL rinse) was injected. Usually, an orange colour developed and black elemental tellurium was precipitated. The mixture was stirred at the specified temperature (see Table 1) for the time indicated and was then filtered by suction through a pad of Celite (2.5 x 2.0 cm) with the aid of diethyl ether (*ca.* 25 mL). The orange filtrate was evaporated at room temperature and the residue was applied in 8:2 hexane–ethyl acetate to a column of ordinary silica gel (1.0 x 15 cm) made up in the same solvent. The material was allowed to penetrate the packing for a distance of about 2 cm. Elution was then stopped for ca. 30 min to allow decomposition of residual tellurium species (deposition of black tellurium), and development was resumed to elute the product, which was obtained pure by removal of solvent and crystallization or distillation. The products were identified by comparison (VPC, TLC, $^1$H NMR) with authentic samples.

**Data on starting materials, dehalogenation method, and reaction products:**

**(1*R*–*endo*)–3–Bromo–1,7, 7–trimethylbicyclo[2.2.1]heptan–2–one (2)**: $^1$H NMR (CDCl$_3$, 90 MHz) $\delta$ 0.93 (s, 3H), 0.97 (s, 3H), 1.07 (s, 3H), 1.20–2.45 (m, 5H), 4.64 (dd, J = 5.0, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 9.7, 19.9, 20.0, 22.5, 30.6, 45.9, 49.7, 53.9, 212.5.

The general procedure was followed using (0.2312 g, 1.0 mmol) of the $\alpha$–haloketone. The reaction was complete after a reflux period of 5 h and pure crystalline *D*–camphor (0.1200 g, 79%) was obtained after chromatography. The material was identical (TLC, $^1$H NMR) with an authentic sample and had $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 0.85 (s, 3H), 0.91 (s, 3H), 0.97 (s, 3H), 1.10–2.65 (m, 7H).

**2–Bromo–3, 4–dihydro–1(2*H*)–naphthalenone (3)**: The bromoketone was purified before use by crystallization from hexane–chloroform: mp 38.5–39.5°C (lit.[37] 40–41°C); IR (neat) 1597, 1683 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 2.00–3.70 (m, 4H), 4.74 (t, J = 4 Hz, 1H), 7.10–8.25 (m, 4H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 26.1, 31.9, 50.6, 127.0, 128.4, 128.8, 129.9, 134.1, 143.0, 190.3.

The general procedure was followed using (0.2251 g, 1.0 mmol) of the $\alpha$–bromoketone. The reaction was complete after 3 h at room temperature and the product was purified by Kugelrohr distillation [bp 150°C, 13 mm)] to afford the ketone (0.1342 g, 91%). The material, which was better than 98% pure (VPC); was identical (TLC, VPC, $^1$H NMR) with an authentic sample and had $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 1.85–3.15 (m, 6H), 7.10–8.20 (m, 4H).

**2–Bromocycloheptanone (4):** The $\alpha$–bromoketone was 99% pure (VPC) and had $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.20–3.10 (m, 10H), 4.67 (dd, J = 9.0, 6.0 Hz, 1 H). The dehalogenation was carried out in the presence of an internal standard (*n*–dodecane) in order to determine the yield by VPC. Three experiments were run following the general procedure but with a different amount of tellurium metal in each case.

Experiment *a:* 1.00 equivalent of tellurium was used. After a reaction period of 3.5 h at room temperature, an aliquot was quenched in water and extracted with ether. The yield of product was 89.6% as judged by VPC measurement.

Experiment *b:* 0.67 equivalent of tellurium was used under the same conditions described in *a*. The yield of product was 78.7% after 1 h at room temperature and reached a maximum of 86.4% after 15 h.

Experiment *c:* 0.14 equivalent of tellurium was used under the same conditions as in *a*. The yield was 67.2% after 5 h and reached a maximum of 69.2% after 8 h.

Cycloheptanone was isolated by chromatography in experiment *a*. The sample was identical with authentic material (TLC, VPC, $^1$H NMR) and had $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 1.55–2.10 (m, 8H), 2.33–2.70 (m, 4H).

**16$\alpha$–Bromo–3–methoxyestra–1, 3, 5(10)–trien–17–one (5):** $^1$H NMR (CDCl$_3$, 100 MHz) $\delta$ 0.94 (s, 3H), 1.35–2.50 (m, 11 H), 2.88 (m, 2H), 3.76 (s, 3H), 4.58 (m, 1H), 6.58–6.80 (m, 2H), 7.20 (d, J = 9.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 14.3, 25.8, 26.5, 29.5, 32.4, 34.0, 37.7, 43.9, 46.3, 47.1, 48.0, 55.2, 111.7, 113.9, 126.3, 131.7, 137.6, 213.1.

Following the general procedure, the $\alpha$–haloketone (0.0457 g, 0.126 mmol) was dehalogenated in 45 min at room temperature. The product (0.0344 g, 96%) was obtained pure after chromatography. It was identical with authentic material and had mp 168–

171.5°C (lit.[50] 164–171°C); $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$ 0.90 (s, 3H), 1.20–2.70 (m, 12H), 1.80–2.00 (m, 2H), 3.76 (s, 3H), 6.56–6.78 (m, 2H), 7.10–7.26 (d, J = 9.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 15.1 MHz) $\delta$ 13.9, 21.7, 26.0, 26.7, 29.8, 31.7, 35.9, 38.5, 44.1, 48.1, 50.6, 55.3, 111.7, 114.1, 126.5, 132.2, 137.9, 157.8, 220.8.

**2,4'–Dibromoacetophenone (6)**: The starting material (Aldrich) was used without further purification. The general procedure using 0.278 g (1.0 mmol) of $\alpha$–bromoketone gave the product after a reaction period of 2.5 h at room temperature. Purification by crystallization from hexane afforded pure 4–bromoacetophenone (0.1562 g, 78.5%). The material was identical (TLC, $^1$H NMR) with an authentic sample and had mp 49–50.5°C (lit.[51] 50–52°C); $^1$H NMR ($CDCl_3$, 60 MHz) $\delta$ 2.50 (s, 3H), 7.45–7.95 (m, 4H).

**2$\alpha$–Bromocholestan–3–one (7)**: $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$ 0.68 (s, 3H), 0.86 (d, J = 3Hz, 6H), 1.08 (s, 3H), 0.70–2.75 (m, 32H), 4.74 (dd, J = 6.5, 3.0 Hz, 1H). The general procedure was followed using 0.0932 g (0.2 mmol) of the $\alpha$–bromoketone. The reaction was complete after 4 h at room temperature. The product (0.0627 g, 81%) was isolated in pure form by chromatography and crystallization. It had mp 127–128.5°C (lit.[59] 128–130°C) and was identical (TLC, $^1$H NMR) with an authentic sample. $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 0.66 (s, 3H), 0.74 (d, J = 6.0 Hz, 6H), 0.99 (S, 3H), 0.60–2.50 (m, 34H).

**2–Bromo–2,4–dimethylpentan–3–one (8)**: The bromoketone was distilled before use and had Bp 75–75.5°C (25 mm) [lit.[55] 59–61°C (18–20 mm)] and $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 1.20 (d, J = 7.0 Hz, 6H), 1.85 (s, 6H), 3.45 (m, J = 6.5 Hz, 1H). The dehalogenation was carried out in the presence of acetophenone as internal standard using 0.1931 g (1.0 mmol) of $\alpha$–bromoketone. The yield, as determined by VPC, reached a maximum of 48% after 3.5 h at reflux temperature. (For VPC examination samples were withdrawn and partitioned between water and ether. The organic phase was then examined by VPC)

**2–Bromocyclohexanone (9):** Distillation before use afforded 2–bromocyclohexanone of 91% purity (VPC). The material had Bp 101.5°C (13 mm) [lit.[54] 78.5°C (5 mm)] and $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.50–2.63 (m, 7H), 2.75–3.20 (m, 1H), 4.45 (dt, J = 5.0, 1.0 Hz, $^1$H).

The general procedure was followed using *n*–dodecane as an internal standard for VPC yield determination and 0.1771 g (1.0 mmol) of $\alpha$–bromoketone. After 2 h at reflux, the yield levelled off at 56% as determined by VPC analysis of aliquots that were removed at intervals and partitioned between water and ether.

**2–Chlorocyclohexanone (10):** The haloketone was purified by distillation. The material was 97.5% pure (VPC) and had Bp 80°C (6 mm) [lit.[53] 90–91°C (14–15 mm)] and $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 1.67–3.10 (m, 8H), 4.20–4.50 (m, 1H).

The $\alpha$–haloketone (0.1326 g, 1.0 mmol) was dehalogenated in the presence of *n*–dodecane as an internal standard following the general procedure. After 7.0 h at reflux temperature, the yield was 36% as judged by VPC analysis of an aliquot that had been partitioned between water and ether.

**2–Chloro–2–methylcyclohexanone (11):** The haloketone was purified by distillation under reduced pressure. The material was 97% pure (VPC) and had Bp 89.5–90°C (25 mm) [lit.[53] 94–96°C (27 mm)] and $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.62 (s, 3H), 1.62–2.50 (m, 7H), 3.75 (dt, J = 13.0, 5.0 Hz, 1H).

The general procedure was followed in the presence of *n*–dodecane as internal standard for VPC yield determination and using 0.1533 g ( 1.04 mmol) of $\alpha$–haloketone. The yield after 15 h at reflux temperature was 19% as determined by VPC analysis.

**2–Chloroacetophenone (12):** 2–Chloroacetophenone (Aldrich) was used without further purification. The general procedure was followed using 0.1546 g ( 1.0 mmol) of $\alpha$–chloroketone. The reaction was complete after 1 h at room temperature and pure acetophenone (0.1010 g, 84%) was isolated after chromatography and Kugelrohr distillation (120°C, 50 mm). The material was identical (TLC, $^1H$ NMR) with an authentic sample and had $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 2.54 (s, 3H), 7.20–7.55 (m, 3H), 7.75–8.00 (m, 2H).

**Evidence for the formation of triethyl phosphate in the dehalogenation of $\alpha$-haloketones:** 2,4'-Dibromoacetophenone (Aldrich) was dehalogenated according to the general procedure (30 min at room temperature) and the reaction mixture was chromatographed over "normal" silica (1.0 x 15 cm) using hexane–ethyl acetate (1:1) as eluant. 4–Bromoacetophenone and triethyl phosphate were both isolated and characterized as follows.

4–Bromoacetophenone had $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 2.57 (s, 3H), 7.50–8.10 (m, 4H); exact mass, m/e 199.9684 (calcd. for $C_8H_7BrO$, m/e 199.9660). It was identical with authentic material (TLC, $^1H$ NMR). Triethyl phosphate had $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 1.35 (dt, J = 7.5, 1.0 Hz, 9H), 4.15 (dq, J = 8.0, 7.0 Hz, 6H); exact mass, m/e 182.0698 (cald. for $C_6H_{15}O_4P$, m/e 182.0708). It was identical with authentic material (TLC, VPC, $^1H$ NMR).

In a second experiment, the yield of triethyl phosphate was determined by VPC using *n*–tetradecane as an internal standard. The experiment was run under conditions identical to those described above. The yield was 100% (VPC).

**Dehalogenation of 2,4'–dibromoacetophenone in the presence of methyl iodide under aprotic conditions:** Tellurium metal (0.2105 g, 1.65 mmol) was placed in a 15–mL round–bottomed flask containing a Teflon coated magnetic stirring bar and equipped with a rubber septum. The flask was purged with argon and a THF solution of sodium diethyl phosphite (1.05 M, 1.62 mL, 1.70 mmol) was added followed by dry THF (3 mL). The mixture was stirred for 5 min at room temperature to produce a clear solution of sodium *O,O*–diethyl phosphorotelluroate. The haloketone (0.4169 g, 1.50 mmol) dissolved in THF (2 mL + 1 mL rinse) was injected. An orange color developed immediately. The solution was stirred for 5 h at room temperature and methyl iodide (0.3 mL, 5 mmol) was then added. The orange solution was stirred 20 h in the dark at room temperature. A white precipitate formed but no tellurium was deposited. The suspension was filtered through Celite and the solvent was evaporated under reduced pressure. The crude red oil that was obtained had $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 1.43 (broad t, J = 7.0 Hz, 6H), 2.59 (s, 1H), 3.25 (s, 1H), 3.85–4.50 (m, 5H), 7.10–8.10 (m, 4H). In this sample only 4–bromoacetophenone and 2,4′–dibromoacetophenone could be identified (TLC, $^1$H NMR).

**Reaction of 2,4′–dibromoacetophenone and sodium *O,O*–diethyl phosphoroselenoate**: Sodium *O,O*–diethyl phosphoroselenoate (0.4570 g, 1.91 mmol) was placed in a 15–mL round–bottomed flask containing a Teflon coated magnetic stirring bar. The flask was equipped with a rubber septum and purged with argon. Absolute ethanol (3 mL) was injected into the flask and the suspension was stirred until all solids had dissolved. 2,4′–Dibromoacetophenone (Aldrich, 0.4447 g, 1.60 mmol) in THF (2 mL + 1 mL rinse) was added to this solution. The mixture slowly became milky. After the reaction was complete (TLC control, 45 min), the solvent was evaporated under reduced pressure and the residue was chromatographed on normal silica gel (1.0 x 15 cm) using 7:4 hexane–ethyl acetate as eluant. A white solid (NaBr?) remained at the top of the column. The major product (Rf 0.33) had IR ($CDCl_3$) 1680, 1587 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 6.0 MHz) $\delta$ 1.35 (t, J = 7.5 Hz, 6H), 4.18 (dq, J = 10.0, 6.0 Hz, 4H), 4.19 (s, 2H), 7.50–8.05 (m, 4H); $^{31}$P ($CDCl_3$, 36.4 MHz) $\delta$ 18.6 (t, $J_{Se-P}$ = 450 Hz), exact mass, m/e 413.9145 (cald for $C_{12}H_{16}{}^{79}BrO_4P^{80}Se$, m/e 413.9135) and was evidently 2–(*O,O*–diethyl phosphoroseleno)–4′–bromoacetophenone. 4–Bromoacetophenone could not be detected in the crude reaction mixture (TLC, $^1$H NMR) before chromatography. Selenium was not precipitated at any stage during the experiment.

**Reaction of 2, 4′–Dibromoacetophenone and sodium diethyl phosphite**: 2,4′–Dibromoacetophenone (Aldrich, 1.4511 g, 5.22 mmol) was placed in a 15 mL round–bottomed flask containing a Teflon–coated magnetic stirring bar. The flask was equipped with a rubber septum and flushed with argon. Ethanolic sodium diethyl phosphite (6 mmol) was added dropwise (syringe). The resulting solution was stirred for 20 h at room temperature and the reaction mixture was then poured into water (50 mL), extracted with ether (3 x 30 mL), washed with water (20 mL) and dried ($MgSO_4$). The solvent was evaporated and the resulting orange oil was chromatographed over normal silica (1.0 x 15 cm) with 8:2 hexane–ethyl acetate. The yield of 4–bromoacetophenone was (0.1910 g, 18%). The material was identical with an authentic sample (TLC, $^1$H NMR).

**Reaction of 2–Chloroacetophenone and sodium diethyl phosphite**: The dehalogenation procedure and scale used were exactly as described above for 2,4–dibromoacetophenone. The yield of acetophenone was 0% after 1 h at room temperature and reached a maximum of 60% after 3 days. The product was identical with an authentic sample (TLC, VPC, $^1$H NMR).

## V. REFERENCES

1. Irgolic, K.J. *J. Organomet. Chem.* 1975, **103**, 91; Irgolic, K.J. *Ibid.* 1978, **158** 235; Irgolic, K.J. *Ibid.*, 1978, **158**, 267; Irgolic, K.J. *Ibid.* 1980, **189**, 65; Irgolic, K.J. *Ibid.* 1980,**203**, 367; Irgolic, K.J. "The Organic Chemistry of Tellurium, " Gordon and Breach, New York, 1974; Irgolic, K.J. In "Tellurium", Copper, W.C., Ed., Van Nostrand–Reinhold New York, 1971; Petragnani, N. de Moura Campos, M. *Organomet. Chem. Rev.* 1967, **2**, 61; Petragnani, N. *Ann. N.Y. Acad. Sci.* 1972, **192**, 10; Houben–Weyl, "Methoden der Organischen Chemie, " Georg Thieme Verlag Stuttgart, 1955, Chapter IX, 917

2. Clive, D.L.J. *Tetrahedron* 1978, **34**, 1049; Reich, H.J. *Acc. Chem. Res.* 1979, **12**, 22

3. Sharpless, K.B.; Gordon, K.M.; Lauer, R.F.; Patrick, D.W.; Singer, S.P.; Young, M.W. *Chem. Scr.* 1975, **8A**, 9

4. Lee, H.; Cava, M.P. *J. Chem. Soc., Chem. Commun.* 1981, 277.

5. Uemura, S.; Fukuzawa, S.–I. *J. Am. Chem. Soc.* 1983, **105** 2748.

6. Otsubo, T.; Ogura, F.; Yamaguchi, H.; Higuchi, H.; Sakata, Y.; Misumi, S. *Chem. Lett.* 1981, 447.

7. Sonoda, N. *Angew. Chem. Int. Ed. Engl.* 1980, **19**, 1009.

8. Kambe, N.; Kondo, K.; Sonoda, N.; *Angew. Chem. Int. Ed. Engl.* 1980, **19**, 1009

9. Ramasany, K.; Kalyanasundaram, S.K.; Shanmugam, P. *Synthesis*, 1978, 545

10. Ramasany, K.; Kalyanasundaram, S.K.; Shanmugam, P. *Synthesis*, 1978, 311.

11. de Moura Campos, M.; Petragnani, N.; Thomé, C. *Tetrahedron Lett.* 1960, **15**, 5.

12. Petragnani, N.; de Moura Campos, M. *Chem. Ber* 1961, **94**, 1759.

13. Engman, L. *Tetrahedron Lett.* 1982, 3601.

14. Chikamatsu, K.; Otsubo, T.; Ogura, F.; Yamaguchi, H.; *Chem. Lett.* 1982, 1081.

15. Barton, D.H.R.; Ley, S.V.; Meerholz, C.A. *J. Chem. Soc., Chem. Commun.* 1979, 755; Ley, S.V.; Meerholz, C.A.; Barton, D.H.R. *Tetrahedron* 1981, **37**, Suppl. 1, 213

16. Ley, S.V.; Meerholz, C.A.; Barton, D.H.R. *Tetrahedron Lett.* 1980, **21**, 1785.

17. Clive, D.L.J.; Anderson, P.C.; Moss, N.; Singh, A. *J. Org. Chem.* 1982, **47** 1641.

18. Kambe, N.; Kondo, K.; Ishii, H.; Sonoda, N. *Bull. Chem. Soc. Jpn.* 1981, **54**, 1460; Kambe, N.; Kondo, K.; Ishii, H.; Murai, S.; Sonoda, N. *Angew Chem. Int. Ed. Engl.*

1979, **18**, 547.

19. Albeck, M.; Tamari, T.; Sprecher, M. *J. Org. Chem.* 1983, **48**, 2276.

20. Engman, L.; Cava, M.P. *J. Org. Chem.* 1982, **47**, 3946.

21. Osuka, A.; Suzuki, H. *Chem. Lett.* 1983, 119.

22. Clive, D.L.J.; Menchen, S.M. *J. Chem. Soc., Chem. Commun.* 1977, 658; Clive, D.L.J.; Menchen, S.M. *J. Org. Chem.* 1980, **45**, 2347.

23. Krief, A.; Denis, J.N. *Tetrahedron Lett.* 1981, 1429.

24. Sharpless, K.B.; Teranishi, A.Y. *J. Org. Chem.* 1973, **38**, 185.

25. Greene, A.E.; Deprès, J.–P. *J. Am. Chem. Soc.* 1979, **101**, 4003; Deprès, J.–P.; Greene, A.E. *J. Org. Chem.* 1980, **45**, 2036.

26. Stork, G.; MacDonald, T.L. *J. Am. Chem. Soc.* 1975, **97**, 1264; Noyori, R.; Hayakawa, Y. "Organic Reactions", Wiley, New York, 1983, Vol. 29, p. 163.

27. Zimmerman, H.E.; Mais, A. *J. Am. Chem. Soc.* 1959, **81**, 3644; Sauers, R.R.; Hu, C.K. *J. Org. Chem.* 1971, **36**, 1153.

28. Kuivila, H.G.; Menapace, L.W. *J. Org. Chem.* 1963, **28**, 2165.

29. Olah, G.A.; Arvanaghi, M.; Vankar, Y.D. *J. Org. Chem.* 1980, **45**, 3531.

30. Goto, T.; Kishi, Y. *Tetrahedron Lett.* 1961, 513.

31. Alper, H.; DesRoches, D. *J. Org. Chem.* 1976, **41**, 806; Alper, H.; Pattee, L. *J. Org. Chem.* 1979, **44**, 2568.

32. Luh, T.-Y.; Lai, C.H.; Lei, K.L.; Tam, S.W. *J. Org. Chem.* 1979, **44**, 641; Alper, H. *Tetrahedron Lett.* 1975, 2257.

33. Borowitz, I.J.; Kirby, K.C. Jr.; Rusek, P.E.; Lord, E. *J. Org. Chem.* 1969, **34**, 2687.

34. Borowitz, I.J.; Grossman, L.I. *Tetrahedron Lett.* 1962, 471.

35. Gemal, A.L.; Luche, J.L. *Tetrahedron Lett.* 1980, 3195; Ho, T.L. *Synth. Commun.* 1979, 241.

36. Townsend, J.M.; Spencer, T.A. *Tetrahedron Lett.* 1971, 137.

37. Olah, G.A.; Vankar, Y.D.; Fung, A.P. *Synthesis* 1979, 59.

38. Ho, T.L.; Olah, G.A. *Synthesis*, 1976, 807.

39. Ho, T.L.; Wong, C.M. *Synth. Commun.* 1973, 237.

40. Ho, T.L.; Wong, C.M. *J. Org. Chem.* 1974, **39**, 562.

41. Giumanini, A.G. *Chimia* 1967, **21**, 464.

42. Clive, D.L.J.; Beaulieu, P.L. *J. Org. Chem.* 1982, **47**, 1124.

43. Foss, O. *Acta Chem. Scand.* 1950, **4**, 1241.

44. Foss, O. *Acta Chem. Scand.* 1947, **1**, 8. Pistschimuka, P. *J. Prakt. Chem.* 1911, **192**, 746.

45. Connor, J.; Van Roodselaar, A.; Fair, R.W.; Strausz, O.P. *J. Am. Chem. Soc.* 1971, **93**, 560.

46. Kipping, F.S.; Pope, W.J. *J. Chem. Soc.* 1893, **63**, 576.

47. Fieser and Fieser, "Reagents for Organic Synthesis," Wiley: New York, 1967, Vol. 1, p. 967.

48. Wilds, A.L.; Johnson, J.A. Jr. *J. Am. Chem. Soc.* 1946, **68**, 86.

49. Paquet, A.; Layne, D.S. *Can. J. Chem.* 1973, **51**, 3855.

50. Johnson, W.S.; Johns, W.F. *J. Am. Chem. Soc.* 1957, *79*, 2005.

51. Rabjohn, N. "Organic Syntheses", Wiley: New York, 1963; Collective Vol. IV, p. 162.

52. Corey, E.J. *J. Am. Chem. Soc.* 1953, **75**, 2301.

53. Horning, E.C. "Organic Syntheses" Wiley: New York, 1955; Collective Vol. III, p. 188.

54. von Schmid, H.; Karrer, P. *Helv. Chim. Acta* 1946, **29**, 573.

55. Sacks, A.A.; Aston, J.G. *J. Am. Chem. Soc.* 1951, **73**, 3902.

56. Brauer, G. "Handbook of Preparative Inorganic Chemistry," 2nd ed., Academic Press: New York, 1963; Vol. I, p. 447; Goldstein, *J. Rev. Chem.* (Bucharest) 1963, **14**(3), 164; *Chem. Abstr.* 1963, **59**, 12425g.

57. Nefedov, V.A. *J. Gen. Chem. USSR Engl.* 1973, **43**, 2002.

58. Chapman and Hall, "Dictionary of Organic Compounds," 5th ed., Vol. I, p. 749.

59. CRC "Handbook of Chemistry and Physics" 55th ed., CRC Press, 1974, p. C239.

60. "Selected Constants; Optical Rotatory Power," la Steroids, Vol. 14, p. 27t; Pergamon: New York, 1965.

61. Krief, A.; Denis, J.N. *Tetrahedron Lett.* 1981, 1431.

62. Kofron, W.G.; Baclawski, L.M. *J. Org. Chem.* 1976, **41**, 1879.

63. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, **43**, 2923.

# CHAPTER 2

# INTRAMOLECULAR RADICAL CYCLIZATIONS

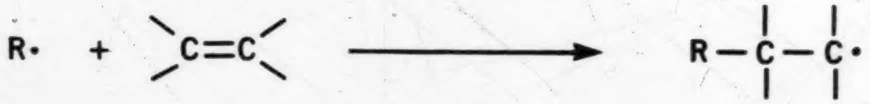
# I. INTRODUCTION

## A. Generalities

Until recently synthetic organic chemists, apart from those involved in the polymer sciences, had given little attention to the use of radicals for making carbon–carbon bonds. It is now becoming increasingly well appreciated that ionic or concerted reactions are not the only ones for this purpose and that free radical chemistry has a great deal to offer in this respect. In the following paragraphs we review the current status of carbon–carbon bond formation by way of free radicals.

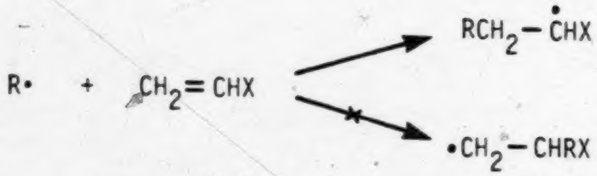
## B. Intermolecular Processes

**a) Mechanistic considerations**: The addition of radicals to unsaturated systems to form a new carbon–carbon bond (equ. 1) has been studied thoroughly and extensive reviews are available on this subject.[1]



(equ. 1)

Alkyl radicals are slightly nucleophilic entities as shown by the increased rate of addition to alkenes carrying an electron withdrawing substituent (CN, COOEt) compared with electron rich olefins.[2] Because of steric repulsion, intermolecular addition of a free radical to a monosubstituted olefin occurs invariably at the unsubstituted end of the double bond (equ. 2). This results in formation of the thermodynamically more stable product (Markownikoff orientation).

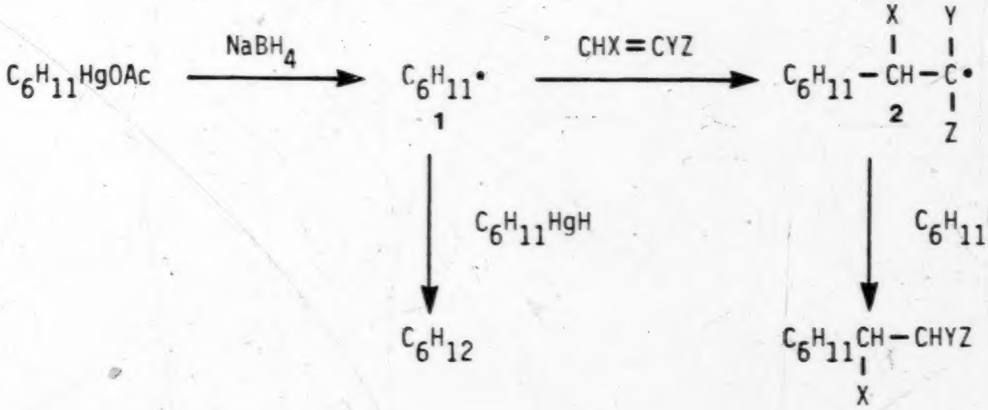


(equ. 2)

The rate of addition is dependent on the polarity of both the attacking radical and the substituent on the double bond.

Radical addition reactions are highly exothermic and MINDO/2 calculations[3] have shown that the transition state occurs very early on the reaction coordinate and is therefore reactant–like in character. As a consequence, delocalization of the unpaired electron in the adduct radical is of little importance in determining the orientation of addition.

**b) Synthetic methods**: Giese and coworkers have long recognized the potential of *intermolecular* radical additions as a method for carbon–carbon bond formation in organic synthesis (equ. 3–12). The idea is based on the fact that alkyl mercurials react with borohydride reducing agents to produce alkyl radicals[4] that can be trapped by electron deficient olefins. In his early work, Giese converted cyclohexylmercuric acetate into cyclohexyl radicals that were captured by a variety of electron deficient alkenes[5] (equ. 3).



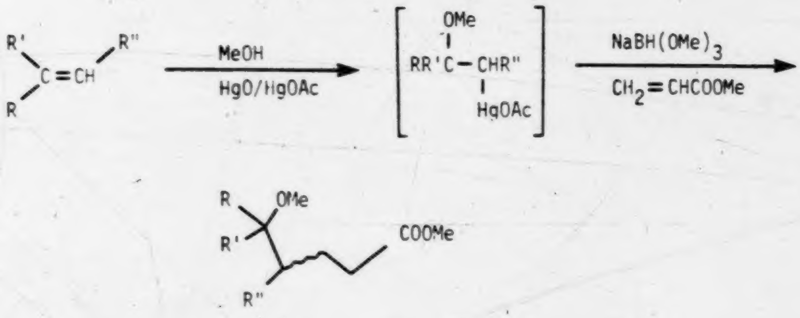
(equ. 3)

The success of the reaction was based on the differences in the rates of the possible pathways: these are adduct **2** formation, capture of cyclohexyl radical **1** by cyclohexyl mercuric hydride, hydrogen transfer to species **2**, and formation of cyclohexyl radical **1** from **2** ($\beta$–fission). Dimerization, disproportionation, polymerization and $\beta$–

bond cleavage of adduct radical **2** evidently did not compete with hydrogen transfer[6] to **2**.

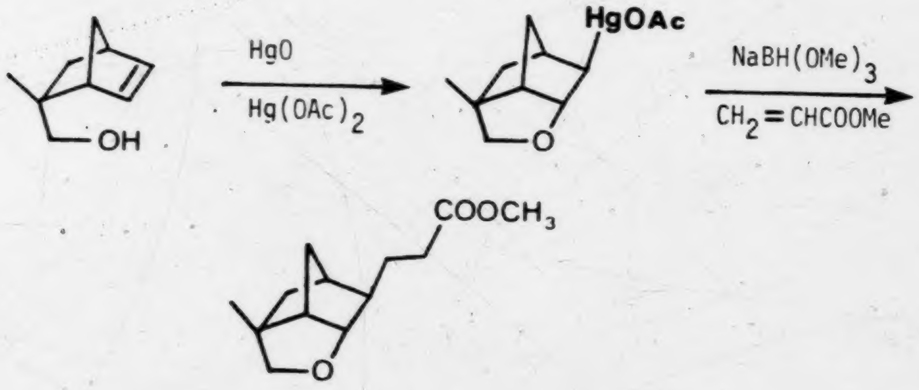
With respect to the addition of alkyl radicals to electron deficient alkenes, polar effects cause the reactivity of the radicals to be opposite to that expected on energetic grounds.[2] In other words, while the order of *reactivity* based on the stability of alkyl radicals would be anticipated to decrease in the series 1° > 2° > 3°, the facts are that in the addition of alkyl radicals to electron deficient olefins, the order is actually: 2° radicals are more reactive than 1° radicals. The classical relationship: high reactivity – low selectivity, is also reversed: 2° radicals are more selective than 1° radicals but they are also more reactive towards addition. Frontier molecular orbital (FMO) theory can explain this behavior as long as steric effects do not come into play.[2,6]

Giese extended his work to the one–flask coupling of alkenes with electron poor olefins via 2–methoxyalkyl radicals[7] (equ. 4).

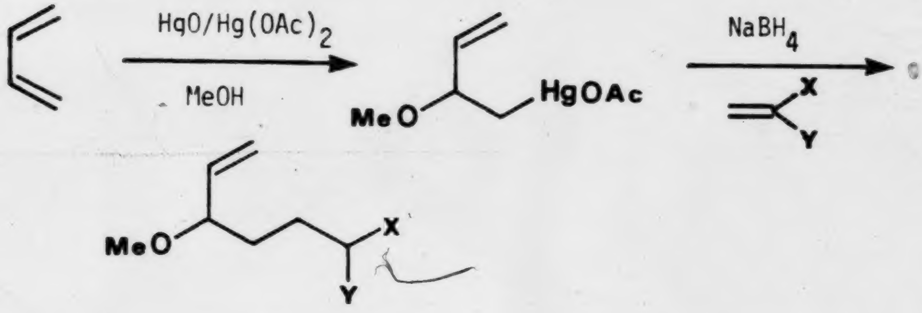


(equ. 4)

Electron rich olefins[8] (equ.5), dienes[9] (equ. 6) and cyclopropanes[10] (equ. 7–10) were also viable substrates in this type of reaction as were maleic acid derivatives (equ. 11).[11]

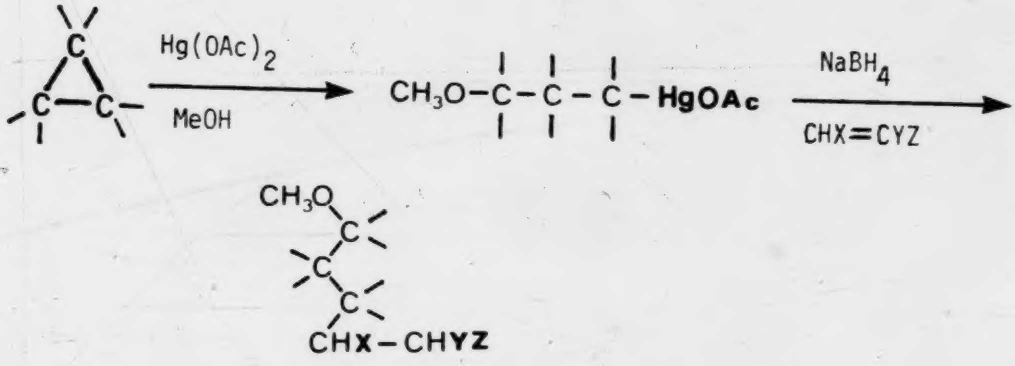


(equ. 5)

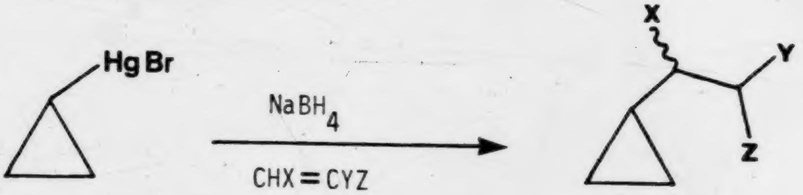

HgO/Hg(OAc)2
MeOH
MeO
HgOAc
NaBH4
X
Y
MeO
X
Y

( 22-60% )

(equ 6)

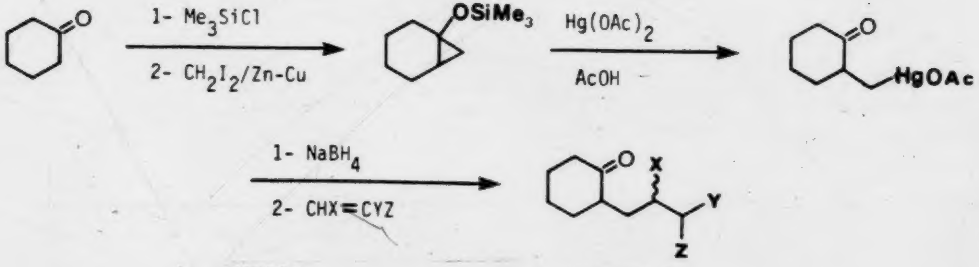

C
C
C
Hg(OAc)2
MeOH
CH3O–C–C–C–HgOAc
NaBH4
CHX=CYZ
CH3O
C
C
C
CHX–CHYZ

(equ 7)


HgBr
NaBH4
CHX=CYZ
X
Y
Z

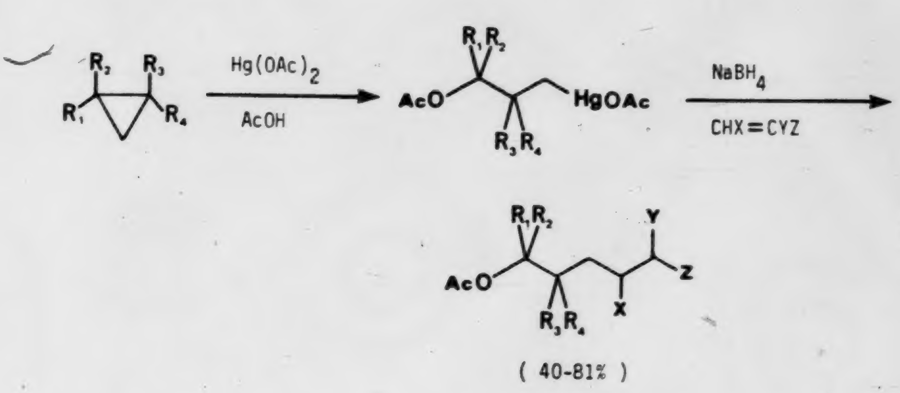
( 53-67% )

(equ 8)

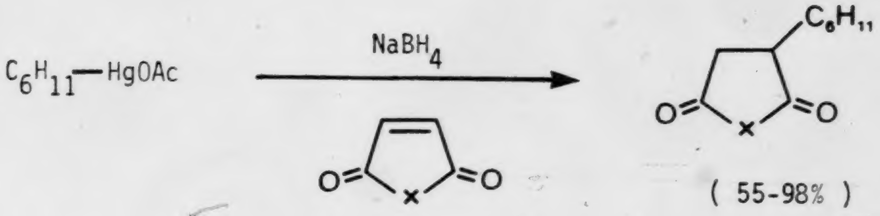

O
1- Me3SiCl
2- CH2I2/Zn-Cu
OSiMe3
Hg(OAc)2
AcOH
O
HgOAc
1- NaBH4
2- CHX=CYZ
O
X
Y
Z

( 50-68% )

(equ 9)



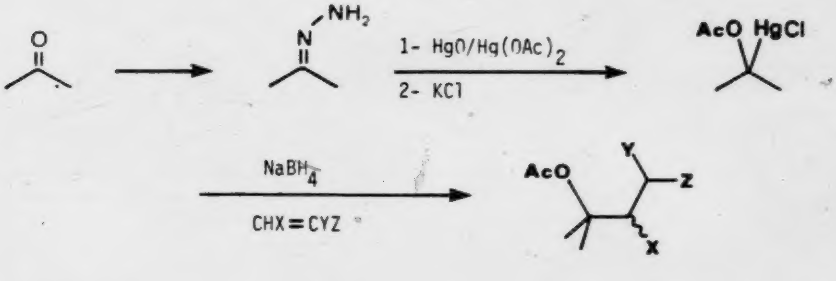
(equ. 10)



(equ. 11)

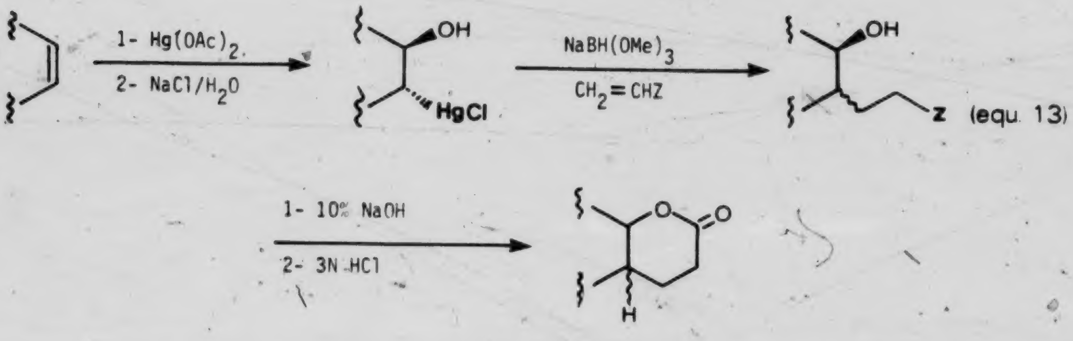
$X = C(CH_3)_2, NCH_3, NH, NPh, S, O$

Most recently, "Umpolung" carbon–carbon bond formation between ketones and alkenes was achieved following the same concept[12] (equ. 12).



(equ. 12)

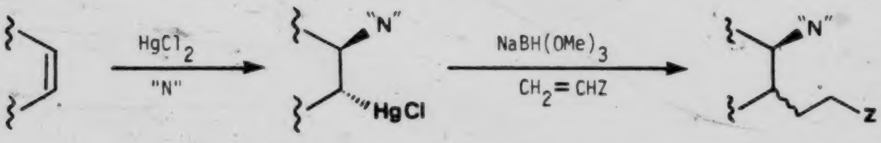
Several other synthetic methods have emerged from the work of Giese. Among them, is a new $\delta$–lactone synthesis which involves the hydromercuration of an alkene followed by a reductive coupling and lactonization[13] (equ. 13).


1- Hg(OAc)2
2- NaCl/H2O
OH
HgCl
NaBH(OMe)3
CH2=CHZ
OH
Z
(equ. 13)
1- 10% NaOH
2- 3N HCl
O
O
H

Z = CN; 60–94%

Z = $COOCH_3$; 37–78%

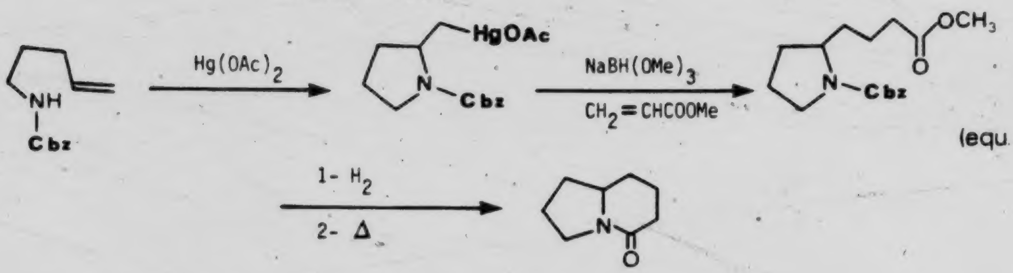
A very useful method for the synthesis of alkaloids is the carbo–amination of a double bond. The elements of "HgCl" and "N" can be added across a double bond and, in certain cases, it is possible to couple the resulting mercurial with electron deficient olefins[14] (equ. 14).


HgCl2
"N"
"N"
HgCl
NaBH(OMe)3
CH2=CHZ
"N"
Z

(equ. 14)

Nitrogen functionalities that were successfully added to the double bond include $NO_2$, $N_3$ and $NHCOCH_3$. However, reductive coupling occurred only with $\beta$–acetamido radicals ("N" = $NHCOCH_3$).

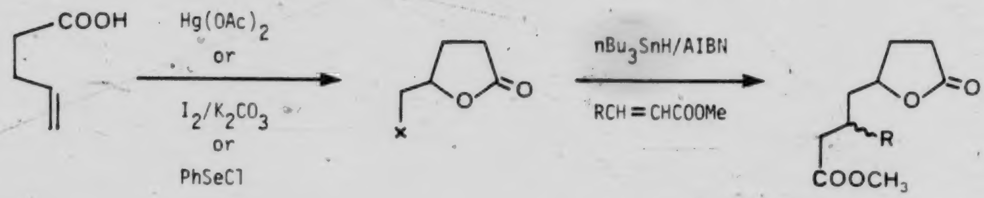
Another procedure for construction of alkaloid skeletons makes use of ureidomercuration and reductive coupling[15] (equ. 15).


Hg(OAc)$_2$
HgOAc
NaBH(OMe)$_3$
CH$_2$=CHCOOMe
OCH$_3$
NH
Cbz
N
Cbz
N
Cbz
O
1- H$_2$
2- Δ
N
O

(equ. 15)

Cbz = $COOCH_2Ph$

$\gamma$–Lactones are an important structural unit in nature and it is desirable to have a variety of methods of functionalizing them. One such procedure uses a radical process and allows for carbon–carbon bond formation[16] (equ. 16).

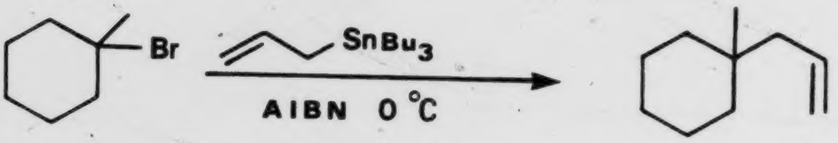

COOH
Hg(OAc)$_2$
or
I$_2$/K$_2$CO$_3$
or
PhSeCl
X
O
O
nBu$_3$SnH/AIBN
RCH=CHCOOMe
O
O
R
COOCH$_3$

(equ. 16)

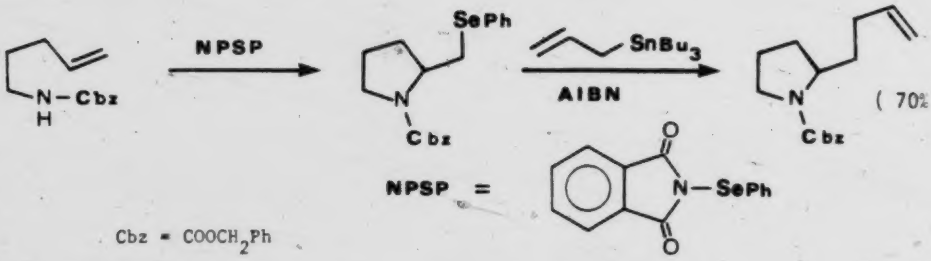
| X | % yield |
|---|---|
| $Hg(OAc)_2$ | 6–58 |
| —I | 45–65 |
| PhSe | 68–80 |

In this case, tributyltin radicals, generated by thermal decomposition of the hydride with azobisisobutyronitrile (AIBN) as initiator, are used to homolyse the C–X bond. The resulting radical is then captured by the electron deficient olefin.

Tin species are useful compounds for generation of radicals. Allyl radicals, for example, are generated conveniently by homolysis of the allylic carbon—tin bond of trialkyl—allyl tins. The process is initiated with AIBN. Alkyl halides[17] (equ. 17), and selenides[11] (equ. 18) can then be chain—extended by a 3—carbon unit. The method is even applicable to hindered substrates such as tertiary alkyl halides and tolerates a variety of other functional groups including acetals, ketals, ethers, epoxides, lactones, hydroxyls, esters, and sulfonates.



(equ. 17)

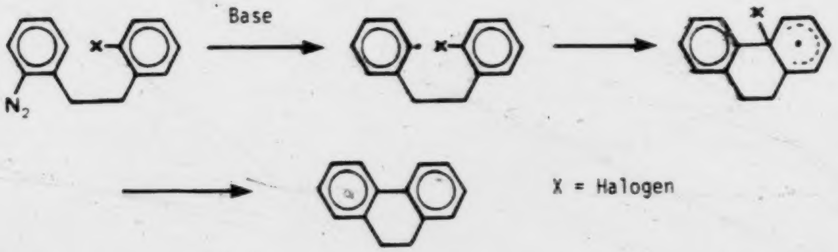


(equ. 18)

Cbz = $COOCH_2Ph$

### C. Intramolecular Processes

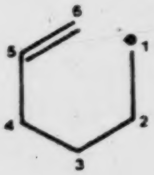
**a) Introduction:** It is conceivable that any reaction capable of forming a carbon—carbon bond can be used intramolecularly to prepare cyclic compounds. This would be a very useful process as most substances that occur in nature incorporate one or more rings or heterocycles in their framework. Until recently, most of the technology available for ring closure was not of the free radical type. In principle, the addition of a radical to an unsaturated entity could be used intramolecularly to close a ring. Furthermore, since oxygen, sulfur and nitrogen radicals can be produced quite easily, a reaction of this type could be used to form heterocycles. Very few examples of such processes of a synthetically useful type have been described in the literature. One of them is the Pschorr phenanthrene synthesis (equ. 19) which proceeds via the radical mechanism shown.



(equ. 19)

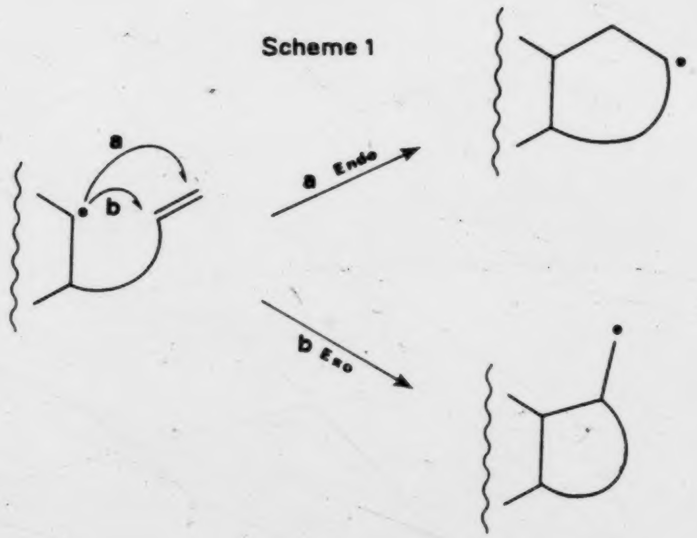
When a long chain alkyl radical contains properly located unsaturation, there exists the possibility for both intermolecular and intramolecular addition, the latter leading to the formation of a ring. The intermolecular process is used industrially for making polymers. If the addition occurs intramolecularly, one can envisage two different modes of attack leading to different ring sizes. As shown in Scheme 1, the radical can attack the double bond at the more substituted terminus (called an *exo*–closure) to give the smaller ring with an exocyclic radical, or addition can take place at the less substituted end of the double bond (*endo*–closure) leading to a larger ring with an endocyclic radical. This type of radical closure has been known for at least 30 years to mechanistic chemists who have studied it in detail, but the reaction has received very little attention as a synthetic method,[16] at least until recently.

**b) The hex–5–enyl radical.** The hex–5–enyl radical **3** is a good example of an acyclic unsaturated radical that undergoes clean intramolecular ring closure.

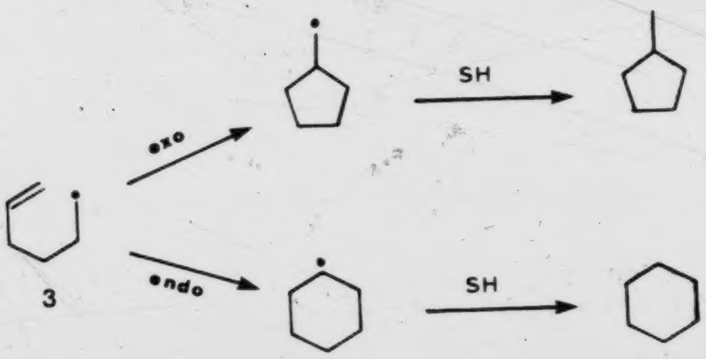


**3**

**Scheme 1**

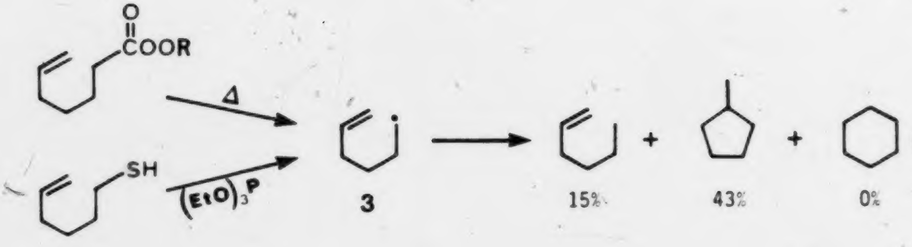


Several factors are involved in determining the regiochemistry of the process. On thermodynamic grounds, (2° radicals being more stable than 1°), one would expect *endo*–closure to predominate. This factor should be reinforced by steric effects (position 6 is less hindered than position 5) and by ring strain which are both expected to favor production of the more stable 6–membered ring (equ. 20).



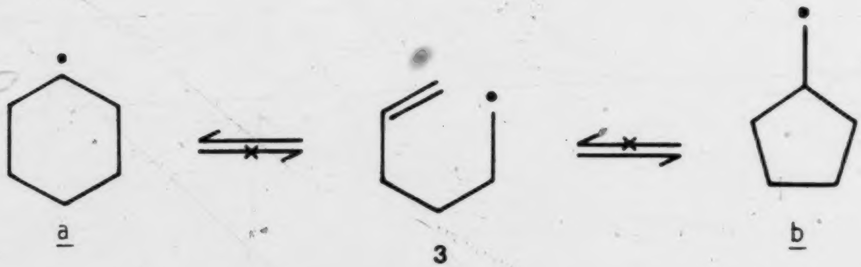
(equ. 20)

Such a line of thought led early workers[20] to report the ring closure of type **3** radicals to cyclohexane derivatives. However, with the advent of better analytical tools, early experiments were reinvestigated[21] and found to be in error. When the hex–5–enyl radical **3** was generated by decomposition of 6–heptanoyl peroxides[21] or by treatment of hexene–6–thiol with triethyl phosphite,[22] no products derived from endocyclic ring closure were detected (equ. 21).



(equ. 21)

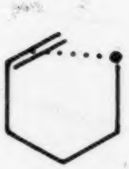
Methylcyclopentane, the result of *exo*—closure was formed as the major product along with 1—hexene, derived by hydrogen transfer to radical **3**. The ring closure was also found to be irreversible[21] (equ. 22).

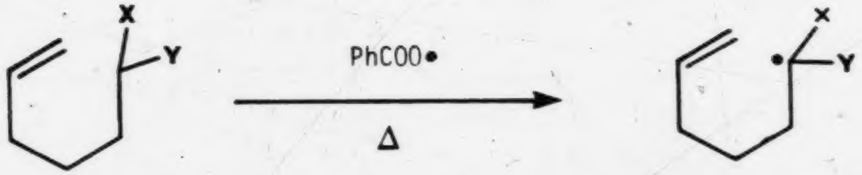


(equ. 22)

Clearly, the relative stability of *a* and *b* was not a determining factor in deciding the course of the reaction. Exclusive formation of the cyclopentane derivative was thought[21] to be a consequence of complexation between the free radical and the double bond as depicted in Fig. 1. However, no acceptable explanation was given[21] as to exactly how the complex caused the reaction to follow the *exo*—pathway. Further evidence bearing on the matter came from the work of Julia and his colleagues. They studied the cyclization of hex—5—enyl radical derivatives such as **4**[23] (equ. 23) in which X and Y are (usually) electron withdrawing groups.

**Figure 1**

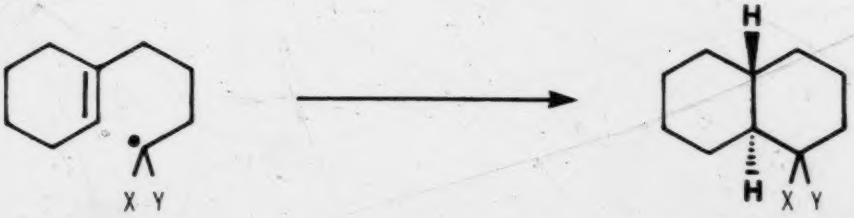




4

(equ 23)

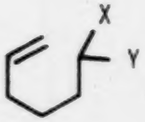
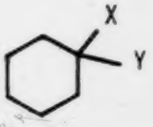
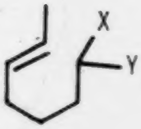
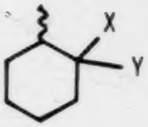
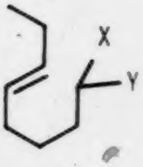
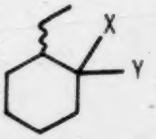
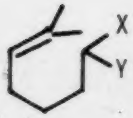
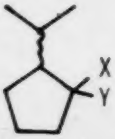
These radicals underwent cyclization in good yield and the results are shown in Table 1[23] (p. 51). The most striking feature is the *endo*–regioselectivity. The yields of cyclized products were found to increase with substitution until the terminal olefinic carbon became fully substituted (entry 4, Table 1). Such substitution caused a drastic fall in the yield of cyclized material and, more importantly, the regioselectivity was completely reversed in favor of *exo*–closure. The reaction was used in a synthetic fashion to construct decalin[24] (equ.24, 25) and tricyclic systems[25] (equ.26).



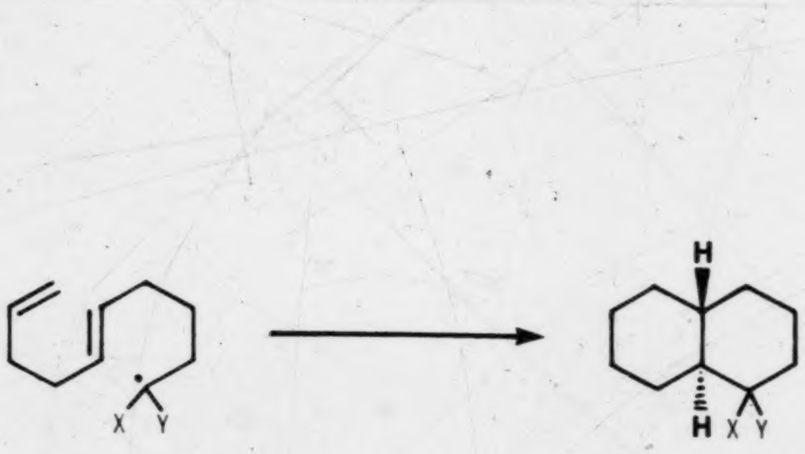
( 47% )

(equ 24)

## TABLE 1
## CYCLIZATION OF HEX-5-ENYL RADICALS CARRYING ELECTRON WITHDRAWING SUBSTITUENTS

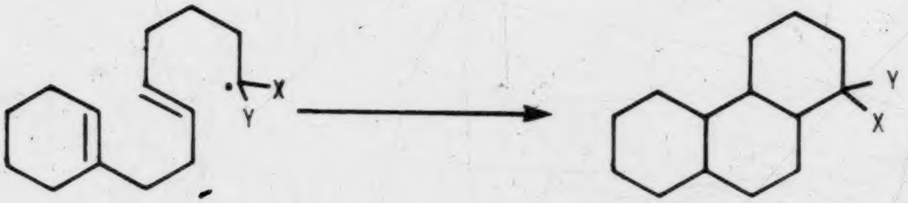
| | Starting Materials | Products | % Yields |
|---|---|---|---|
| 1 |  |  | 51 |
| 2 |  |  | 65 |
| 3 |  |  | 78 |
| 4 |  |  | 13.5 |

X = CN, Y = COOEt



( 41% )

(equ. 25)



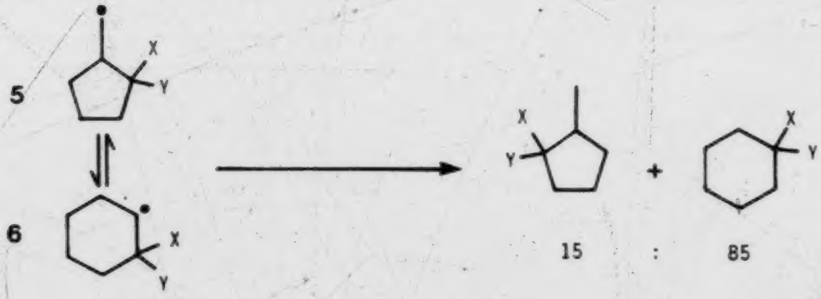
( 26% )

(equ. 26)

X = CN ; Y = COOEt

The regioselectivity of the reaction (*exo*– vs *endo*–) was altered by modifying the stability of the initial radical **4**. This was done by changing the nature of substituents X and Y[26] (Table 2, p. 53).

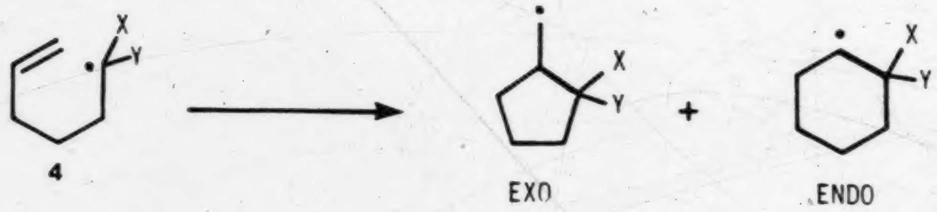
An important factor in rationalizing the regiochemistry was the realization that cyclization of radicals of type **4** is reversible[27] (equ.27). In crucial experiments, Julia showed that both radicals **5** and **6**, when prepared independently, gave the same equilibrium mixture of methylcyclopentane and cyclohexane derivatives in a ratio of 15:85. This ratio was identical to the one obtained from closure of the acyclic radical **4** (X = CN, Y = COOEt; See Table 2).



15 : 85

(equ 27)

## TABLE 2
## *EXO/ENDO* RATIOS IN THE CYCLIZATION OF 4

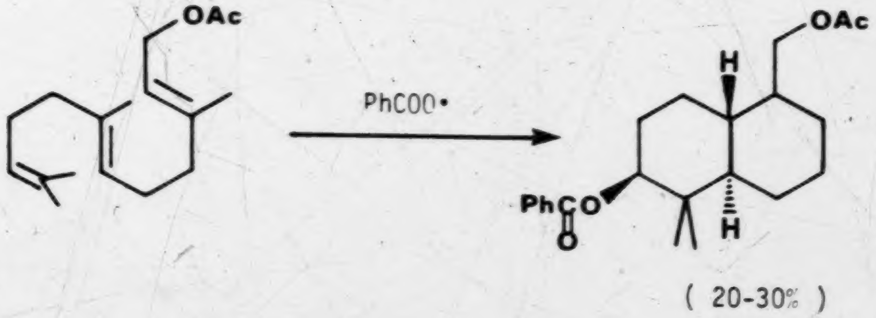

X
Y
4
X
Y
EXO
X
Y
ENDO

| | X | Y | Relative Yields % | |
|---|---|---|---|---|
| 1 | H | H | 100 | 0 |
| 2 | Ph | H | 90 | 10 |
| 3 | COOEt | COOEt | 60 | 40 |
| 4 | COOEt | CN | 16 | 84 |
| 5 | X, Y | = 0 | 0 | 100 |

In other words, exocyclic closure occurs under kinetic control for the values of X, Y= H (see Table 2, entry 1). If the reaction is made reversible by stabilizing the initial radical **4** (X = CN, Y = COOEt or Ph[30]), products derived from the endocyclic mode are formed under thermodynamic control.

It was suggested by Capon in 1964, as a result of studying molecular models, that *exo*–ring closure occurs under kinetic control because the number of available conformations in which attack at position 5 is possible is greater than that for attack at position 6.[28] Subsequently, Julia and Lebel[27] proposed a stereochemical argument according to which cyclohexane formation is hindered by steric interaction between a hydrogen at C–2 and the *syn*–hydrogen on C–6 in the transition state leading to *endo*–ring closure[29] (Fig. 2). Ring closures of 1° radicals (such as **3**) are not reversible and exclusive formation of exocyclic products is to be expected (see above, discussion related to equ. 27) under kinetic control.[21]

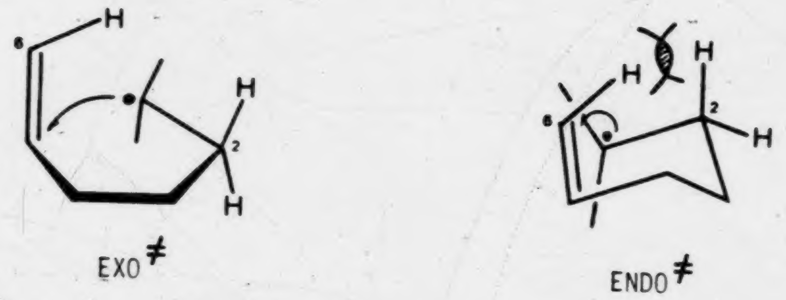
Several other isolated cases of radical cyclizations operating in the *endo*–mode are known. For example, addition of benzoyloxy radicals to farnesyl acetate results in a low yield of a *trans*–decalin system[31] (equ. 28).

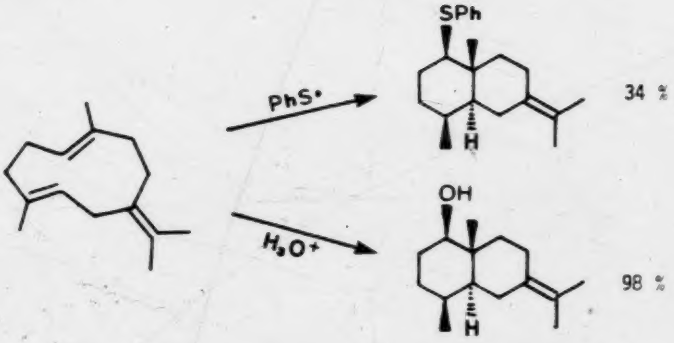


(equ. 28)

The reason for the observed regiospecificity is not known. Germacrene, when treated with thiyl radicals undergoes cyclization with stereo– and regiospecificity similar to that observed in electrophilic cyclizations of the same substrate[32] (equ. 29).

Figure 2





(equ. 29)

A reaction that made an indirect, but important, contribution to the study of radical closure was a procedure developed by Kuivila for homolysis of carbon—halogen bonds. It provided a clean and efficient source of radicals[33] and allowed easy access to 3. The method involves trialkyltin hydride reduction of alkyl halides (equ. 30).

$$R_3SnH \xrightarrow[\text{AIBN}]{\Delta} R_3Sn\cdot \qquad \text{Initiation}$$

$$R_3Sn\cdot + R'X \xrightarrow{S_H2} R_3SnX + R'\cdot$$

(equ. 30)

Propagation

$$R'\cdot + R_3SnH \xrightarrow{S_H2} R'H + R_3Sn\cdot$$

The tin hydride reduction was applied to 6–bromo–1–hexene and the resulting radical was found[34] to close almost exclusively in an exocyclic fashion to give methylcyclopentane (81.1%), cyclohexane (1.6%) and 1–hexene (17.3%) (Scheme 2, p. 57). The absence of dimerization and disproportionation is a consequence of the ease of abstraction of a hydrogen atom from trialkyltin hydrides.[35] The formation of 1–hexene results from rapid hydrogen transfer to radical **3**. The yield of cyclization products was found to be dependent on temperature[36] and tin hydride concentrations.[34] Similarly, the *exo/endo* ratio is dependent on the temperature and the stability of radicals of type **3**.[36]

To account for preferential formation of the less stable *exo*–product, a new proposal was made that there exists a more favorable entropy of activation for production of a 5–membered ring versus a 6–membered ring.[37] Theoretical calculations[38] estimated the difference in entropy of activation for the two processes as 3.3 cal mol$^{-1}$ °K in favor of the former. The importance of this factor was questioned[39] since enthalpy of activation differences between the two modes of cyclization are of far greater magnitude[39] (1.7 kcal/mol). The entropy difference is much too small to account for the *exo*–selectivity that is observed.[34] The enthalpy of activation calculated[38] for exo– and endo–cyclic ring closure for unsaturated carbon radicals is depicted in Figure 3. From this diagram one would expect allyl, but–3–enyl, and pent–4–enyl radicals to undergo preferential exocyclic ring closure as the enthalpy of activation is more favourable than for *endo*–closure. Based on enthalpy considerations alone, the hex–5–enyl radical can undergo closure via either mode and radicals where *n* is larger than 4 should show a preference for the endocyclic pathway. Clearly, the experimental results differ from these predictions and enthalpy of activation cannot be the only factor involved.

The hypothesis of Julia and Lebel, which invoked steric considerations has already been discussed for cyclization of cyano–carboxylate substituted radicals **4**.[29,40] As shown in Figure 4 (p. 58), when applied to a simple 5–hexenyl radical, there is seen to be a non–bonded interaction between the pseudo–axial proton at C–2 and the *syn*– proton at C–6. This destabilizes the transition state lying on the path to *endo*–cyclization. The models for these transition states are based on the structure of the hex–5–enyl radical **3** which was suggested by EPR spectroscopy.[41] In support of these steric arguments were the measurements on *exo/endo* ratios determined for a variety of substituted hex–5–enyl

Scheme 2

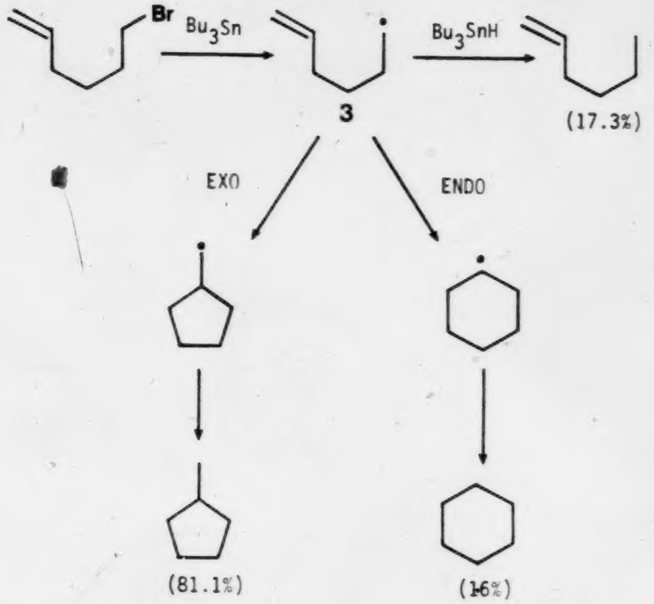

Br
$Bu_3Sn$
$Bu_3SnH$
3
(17.3%)
EXO
ENDO
(81.1%)
(1.6%)

Figure 3

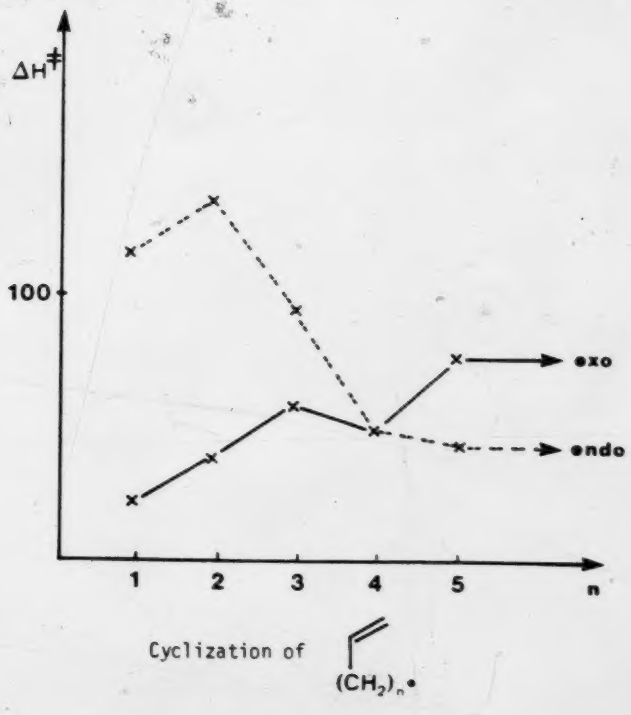
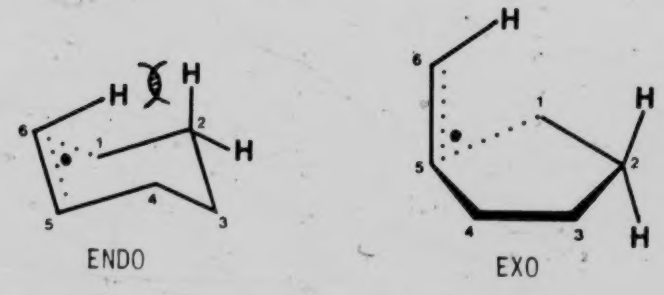


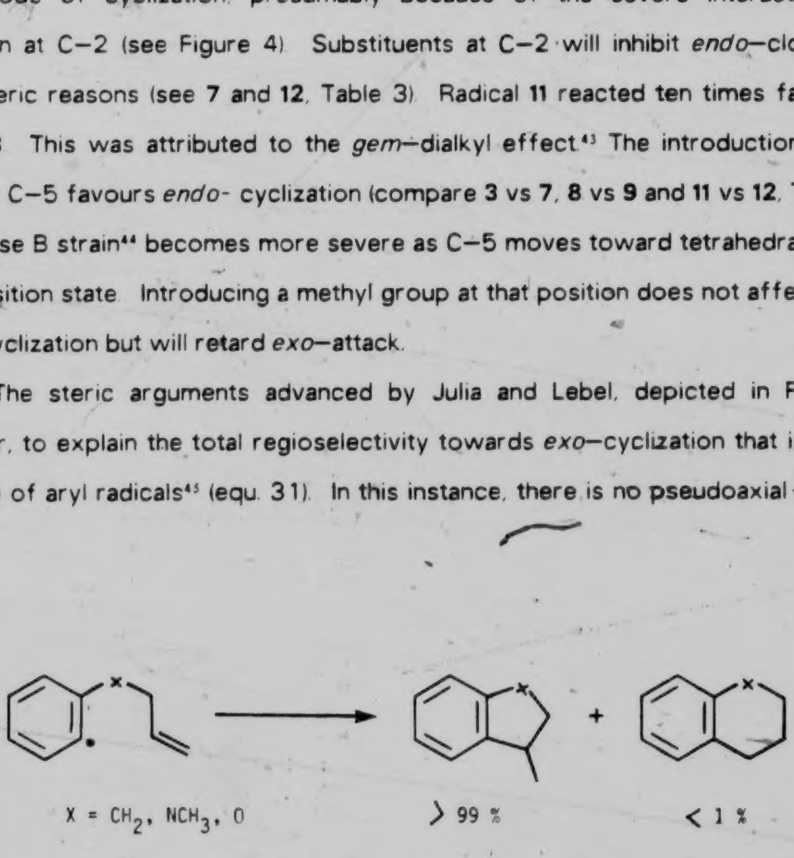
Figure 4



ENDO EXO

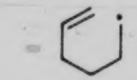
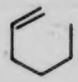
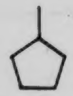
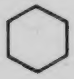
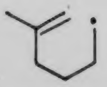
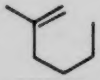
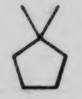
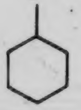
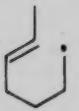
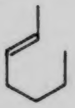
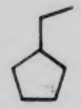
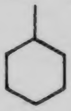
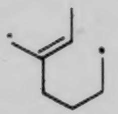
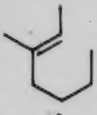
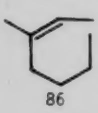
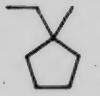
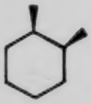
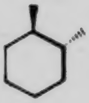
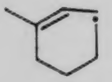
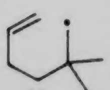
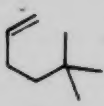
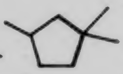
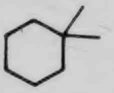
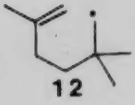
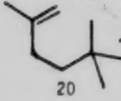
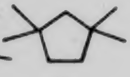
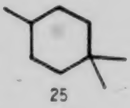
radicals[40-42] (Table 3, p. 59). The conclusions that can be derived from Table 3 are as follows: A *syn* methyl group at C–6 (as in **10**, Table 3) results in total inhibition of the *endo*–mode of cyclization, presumably because of the severe interaction with the hydrogen at C–2 (see Figure 4). Substituents at C–2 will inhibit *endo*–closure for the same steric reasons (see **7** and **12**, Table 3). Radical **11** reacted ten times faster than the parent **3**. This was attributed to the *gem*–dialkyl effect.[43] The introduction of a methyl group at C–5 favours *endo*- cyclization (compare **3** vs **7**, **8** vs **9** and **11** vs **12**, Table 3). This is because B strain[44] becomes more severe as C–5 moves toward tetrahedral geometry in the transition state. Introducing a methyl group at that position does not affect the rate of *endo*-cyclization but will retard *exo*–attack.

The steric arguments advanced by Julia and Lebel, depicted in Figure 4, fail, however, to explain the total regioselectivity towards *exo*–cyclization that is observed in the case of aryl radicals[45] (equ. 31). In this instance, there is no pseudoaxial substituent at C–2!



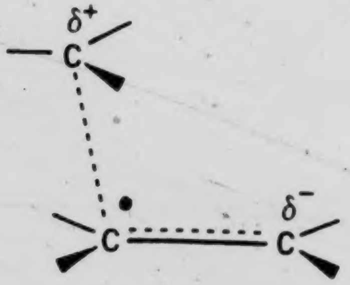
(equ 31)

## TABLE 3
## CYCLIZATION OF ALKYL SUBSTITUTED 5-HEXENYL RADICALS

| RADICAL | PRODUCTS (%) | | | | | EXO:ENDO |
|---|---|---|---|---|---|---|
| <br>**3** | <br>17 | <br>81 | <br>2 | | | 40:1 |
| <br>**7** | <br>84 | <br>4.5 | <br>11.5 | | | 1:2.6 |
| <br>**8** | <br>51 | <br>46 | <br>0 | | | 46:0 |
| <br>**9** | 77<br> | 2.5<br> | 7.5<br> | 4<br> | 9<br> | 1:1.7 |
| <br>**10** | 2 | 86 | 12 | 0 | 0 | 12:0 |
| <br>**11** | <br>6 | <br>94 | <br>0 | | | 94:0 |
| <br>**12** | <br>20 | <br>55 | <br>25 | | | 2.2:1 |

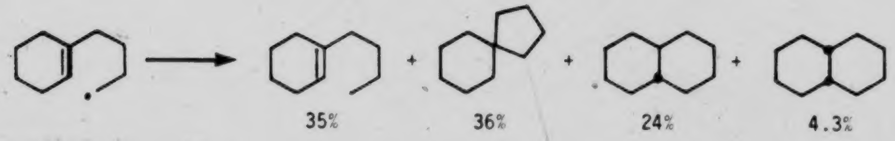
By the mid–nineteen seventies, it was finally appreciated that most of the observations could be accounted for satisfactorily by concepts of stereoelectronic control. The structure of the transition state for alkyl radical additions to double bonds was proposed to comprise a triangular array of centers arising from the initial interaction of the semi-occupied 2*p* orbital with one lobe of the vacant $\pi^*$ orbital.[45] Consequently, the transition complex is dipolar (Figure 5).

**Figure 5**

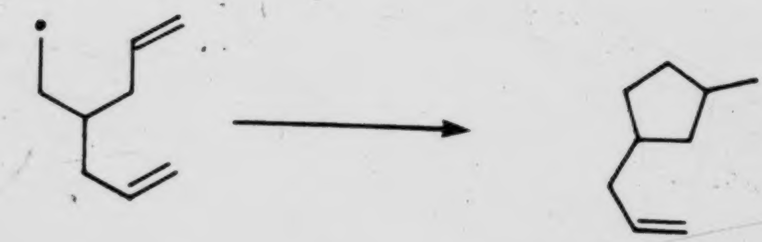


The degree to which this arrangement can be achieved by the three atoms involved determines the ratio of *exo*/*endo* cyclization.

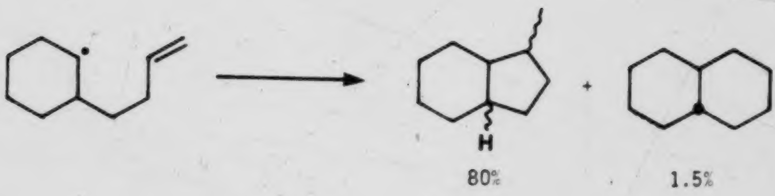
These arguments proved useful in explaining a number of experiments. In each case, the extent of *exo*– or *endo*–cyclization is determined by the relative ease of accommodating the transition state, depicted in Figure 5, for each mode. For example, the behavior of the 4–(1–cyclohexenyl)butyl[46] (equ. 32), the 3–allylhex–5–enyl[47] (equ. 33) and the 2–(but–3–enyl) cyclohexyl radicals[49] (equ. 34) is considered to be under stereoelectronic control and an examination of molecular models suggests that the planar array (Fig. 5) is not easily accessible for *endo*–closure.



(equ. 32)

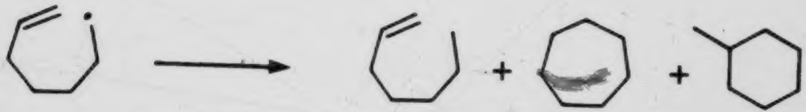


(equ. 33)

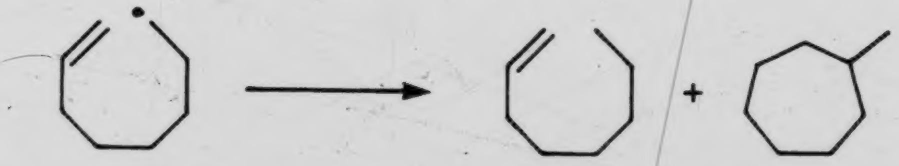


(equ. 34)

The theory also applies to cyclization of hept–6–enyl (equ. 35) and oct–7–enyl radicals[41] (equ. 36).

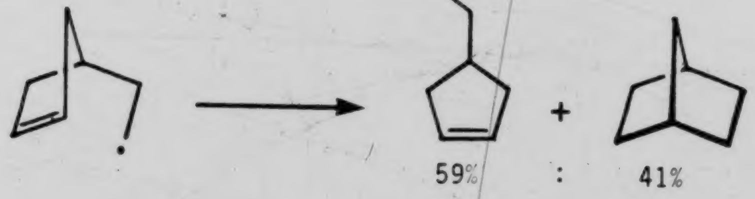


(equ. 35)



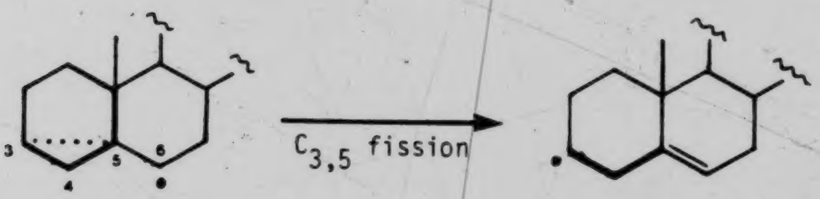
(equ. 36)

Radical ring closures also occur in cases where strained systems are generated such as in the cyclization of 2–($\Delta^3$–cyclopentenyl)ethyl bromide[50] (equ. 37).



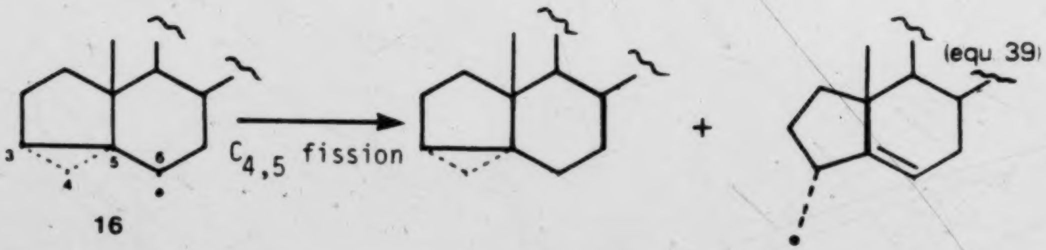
(equ. 37)

The theory of stereoelectronic control is applicable to the reverse process, i.e., radical fragmentations[51] (equ. 38, 39).



**15**

(equ. 38)

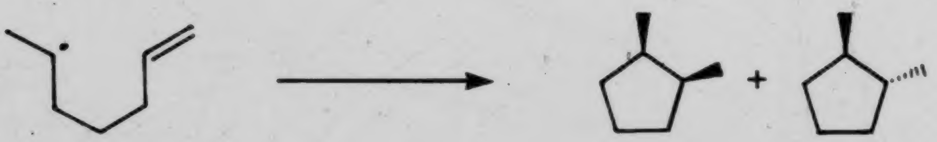


**16**

(equ 39)

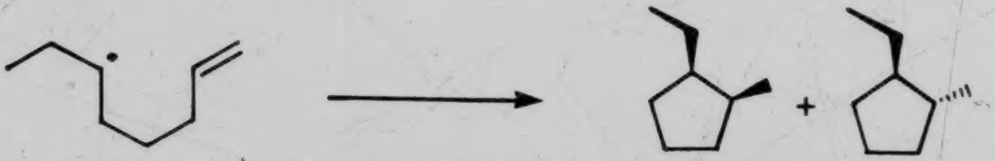
The two radicals **15** and **16** undergo regiospecific fragmentation. In each case, the bond which lies most nearly parallel to the axis of the half–filled *p*–orbital at C–6 is cleaved preferentially. The relative stabilities of the intermediate radicals is not involved.

Because 1,5–cyclization of *substituted* hex–5–enyl radicals leads to cyclopentane derivatives having substituents around the periphery of the ring there is the possibility of *cis*– and *trans*– isomerism. There is a relationship that links the substitution pattern of the hex–5–enyl radical and that of the cyclized product. For example, 6–hepten–2–yl radicals undergo 1,5–ring closure to 1,2–disubstituted cyclopentanes in which the proportion of *cis*–isomer predominates[52] (equ 40–42).



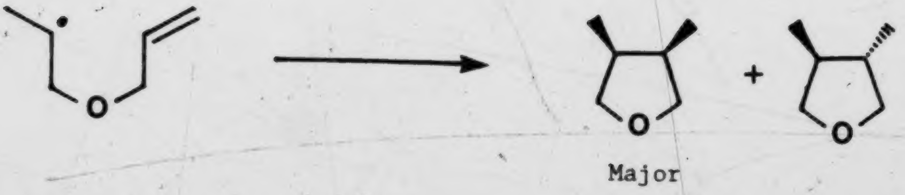
(equ 40)

Major



(equ 41)

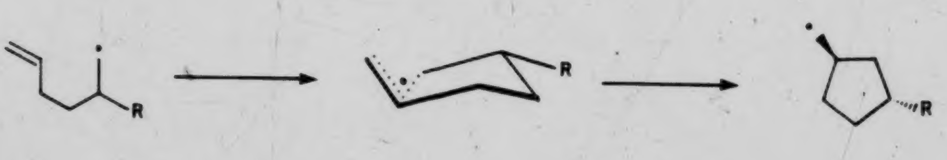
Major



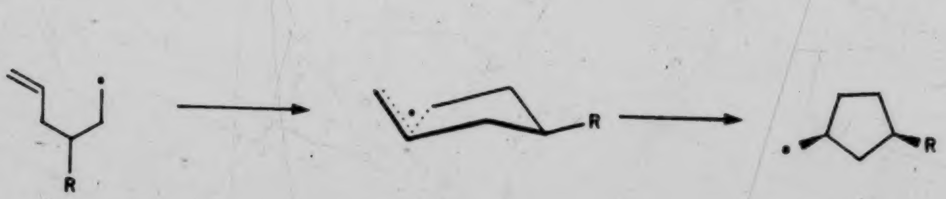
(equ 42)

In each case, the *cis/trans* ratio was 2.3. The preferential formation of *cis*–products has been attributed to the effects of orbital symmetry. The two transition states leading to *trans*– and *cis*–1,2–disubstituted cyclopentanes respectively are depicted in Figure 7. In the transition state for *cis*–products there is a secondary attractive interaction between the alkyl substituent and the olefinic bond. This factor does not apply to the transition state leading to *trans*–1,2–disubstituted cyclopentanes. As pointed out by Hoffmann[53] such interactions become important in highly exothermic processes such as radical additions to double bonds.

In the case of C–2, C–3 and C–4 substituted hex–5–enyl radicals, the degree of stereoselectivity is related to the conformational preference of the substituents[54] as shown in equations 43–45.

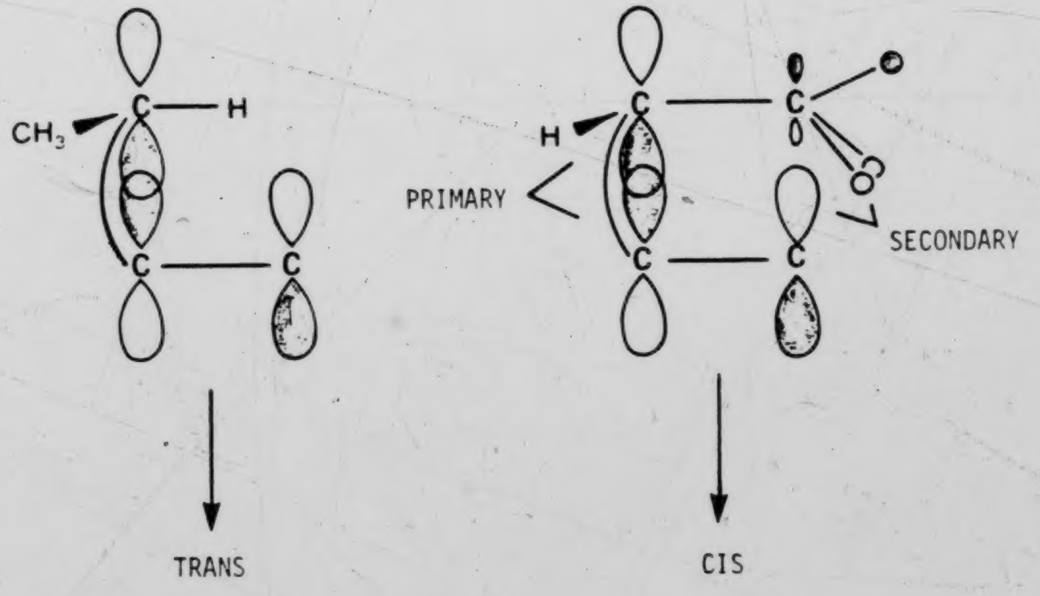


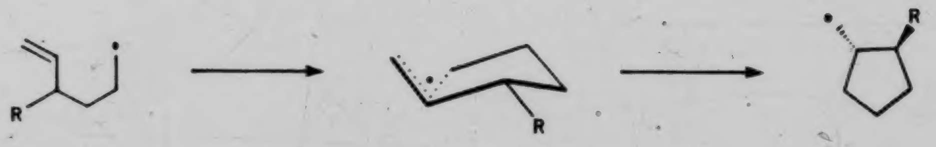
(equ 43)



(equ 44)

Figure 7


CH$_3$
C
H
C
C
PRIMARY
SECONDARY
Co
TRANS
CIS

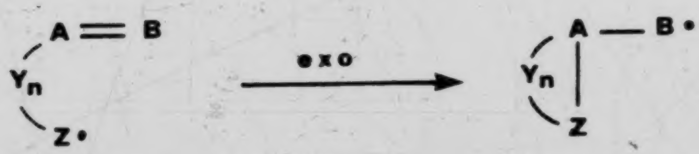


(equ. 45)

The stereoselectivity is explained by a chair–like conformation with substituents occupying *pseudo*–equatorial positions. The degree of selectivity increases as the substituents become more bulky.

A set of guidelines for radical cyclizations is now available to help predict the outcome of such reactions.[55]

1. Radical intramolecular additions to C=C and C≡C under kinetic control occur preferentially in the *exo*— mode for $3 \leq n \leq 5$ (equ. 46).

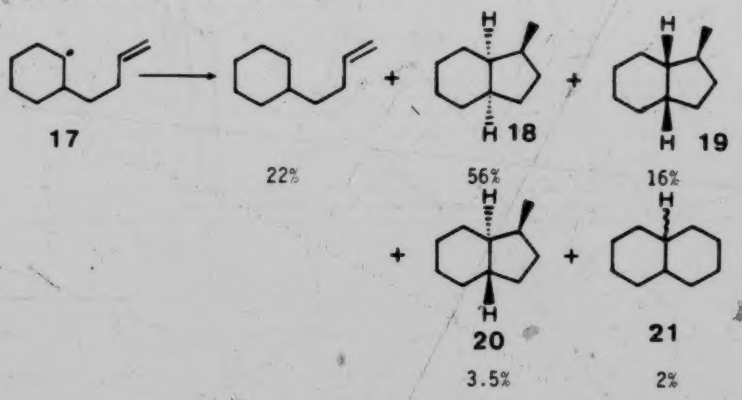


(equ. 46)

For n larger than 5, the flexibility of the chain increases to the point where attack of the terminal unsubstituted carbon becomes preferred (as in intermolecular additions). For systems under thermodynamic control, or substituted at atom A, (equ.46), *endo* cyclization is favoured.

2. Substituents on the olefinic bond retard the rate of addition at that position. This effect can lead to a reversal of regiospecificity.
3. Sustituted hex—5—enyl radicals undergo stereoselective ring closure. C—1 or C—3 substituted systems give mainly *cis*—products whereas C—2 or C—4 substituted systems give mainly *trans*—products.

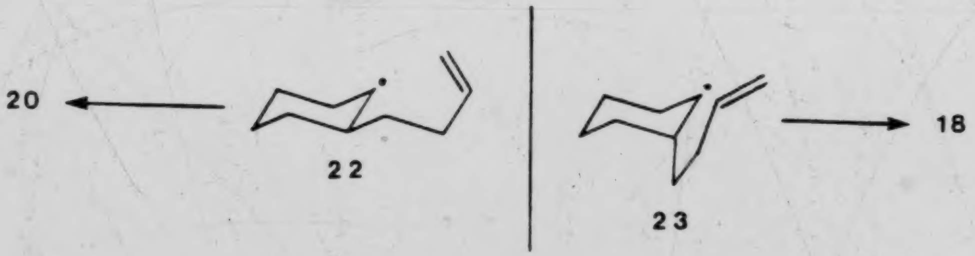
Other factors can modify these guidelines and a case in point is the result with the 2—(but—3—enyl)cyclohexyl radical **17** (equ. 47).[56]



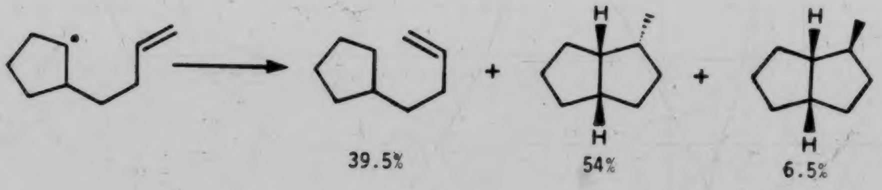
(equ. 47)

Radical **17** is formally a 1,2–disubstituted hex–5–enyl radical. According to the guidelines, **20**, where the methyl group is *cis* to the "C–1" substituent and *trans* to the "C–2" substituent, should be the favoured product. In the event all *cis* isomer **18** is formed preferentially. Production of **18** is explained by taking into account the steric constraints applied by the ring. These are not present in acyclic systems (Fig. 8).

**Figure 8**

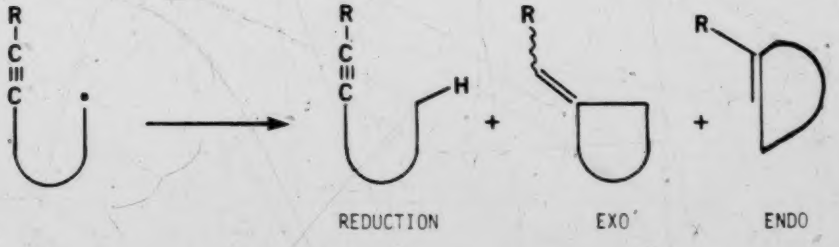


Radical **22** allows poor overlap of the semi–occupied *p* orbital and the antibonding π* orbital. When the substituent is placed in an axial position as in **23**, maximum interaction occurs. Species **23** affords *cis*–fused products of which **18** (where the methyl group is *cis* to the C–1 substituent) is the major as predicted by the guidelines. It is also expected that **20** should be the major isomer when the 3–butenyl substituent is in an equatorial position as in **22**. Similar results have been observed in the cyclization of the cyclopentane analogue[57] (equ. 48).



(equ. 48)

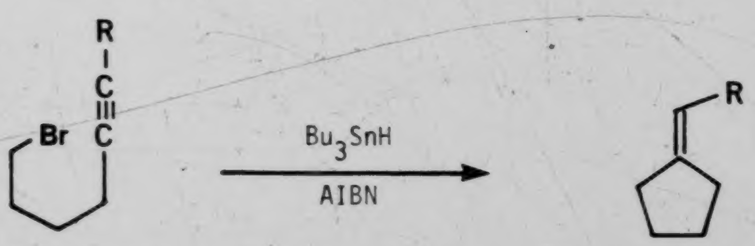
**c) Intramolecular cyclization of radicals onto triple bonds.** Like alkenyl radicals, alkynyl radicals can undergo exo– or endocyclic ring closure[51] (equ. 49).



(equ 49)

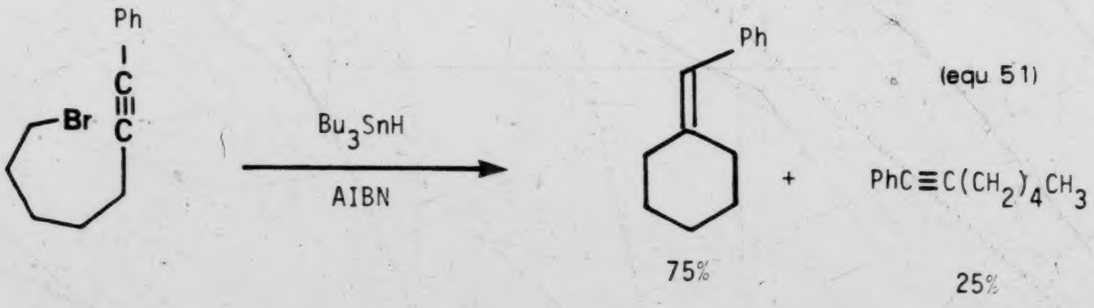
This type of radical cyclization has not been studied as extensively as its double bond counterpart. This is surprising because the process is much more useful synthetically. In the case of hex–5–enyl radicals, functionality (here the C=C bond) is destroyed in the cyclization. With acetylenes, however, the carbon–carbon triple bond is converted to a double bond which is then available for further manipulation.

The factors governing cyclizations onto double bonds appear to apply to acetylenic radicals as well. *Exo*–cyclization is kinetically preferred over the *endo*– mode as shown in equations 50–52.[51] (It is assumed that these reactions are irreversible.)

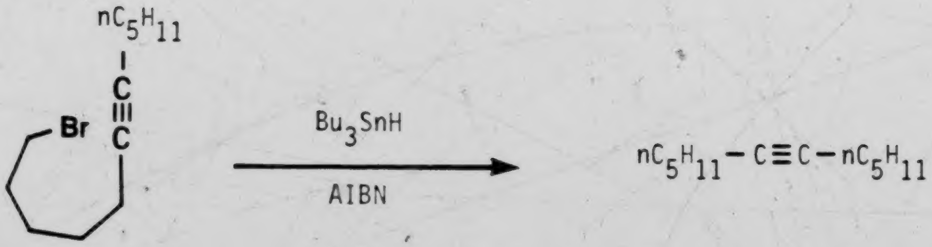


(equ. 50)

R = $C_5H_{11}$, Ph

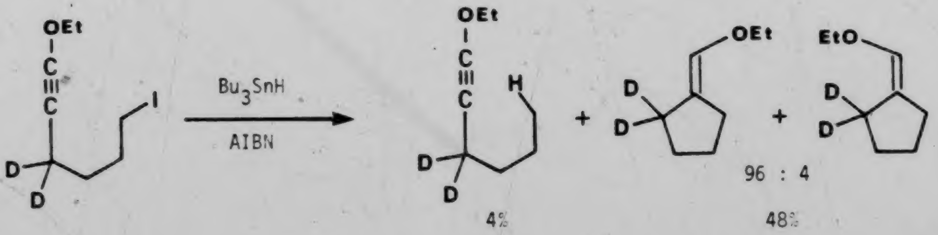

Ph
Br
Bu3SnH
AIBN
Ph
+
PhC≡C(CH2)4CH3
75%
25%

(equ 51)


nC5H11
Br
Bu3SnH
AIBN
nC5H11−C≡C−nC5H11

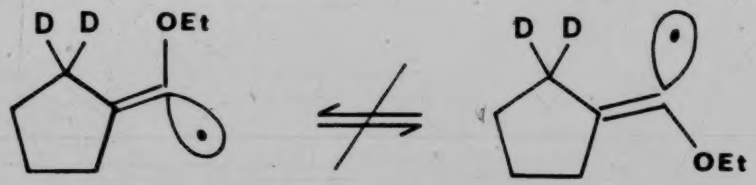
(equ 52)

The proportion of cyclization versus reduction is determined by the rate of hydrogen abstraction by the original radical, a factor that is controllable by the concentration of tin hydride. The radical cyclization takes place stereoselectively in the *anti*–fashion where the half–filled $sp^2$ hybrid orbital is situated *trans* to the added group[59] (equ. 53).


OEt
I
D
D
Bu3SnH
AIBN
OEt
H
D
D
4%
+
OEt
D
D
+
EtO
D
D
96 : 4
48%

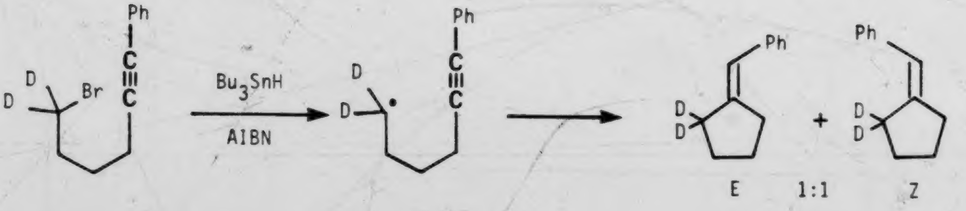
(equ. 53)

This observation indicates that the cyclized vinylic radical does not undergo rapid isomerization (equ. 54).


D D
OEt
D D
OEt

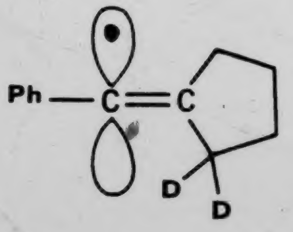
(equ. 54)

In the case of a phenyl–substituted acetylene, where stabilization occurs through delocalization of the odd electron into the benzene ring, there is evidence for the occurrence of linear 1–phenylvinylic radicals[60] (equ. 55).



(equ 55)

The presence of equal amounts of (*E*) and (*Z*) isomers is consistent with of the intermediacy of linear vinylic radical **24**.

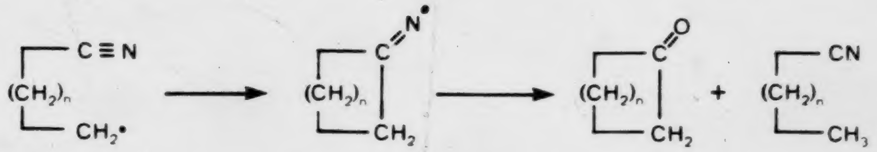


**24**

Radicals are also known to undergo regiospecific *exo*–ring closure onto the C ≡ N triple bond of a nitrile group.[61] Hydrolysis of the intermediate imine leads to the corresponding cycloalkanone (Table 4).

Because of differences in activation energy, the intramolecular cyclization of a radical onto a C≡N is slower than the corresponding cyclization onto a C=C or a C≡C[62] (Table 5). The synthetic possibilities of $\delta$–cyano–radicals do not appear to have been recognized.

## TABLE 4
## CYCLIZATION OF ω-CYANO RADICALS



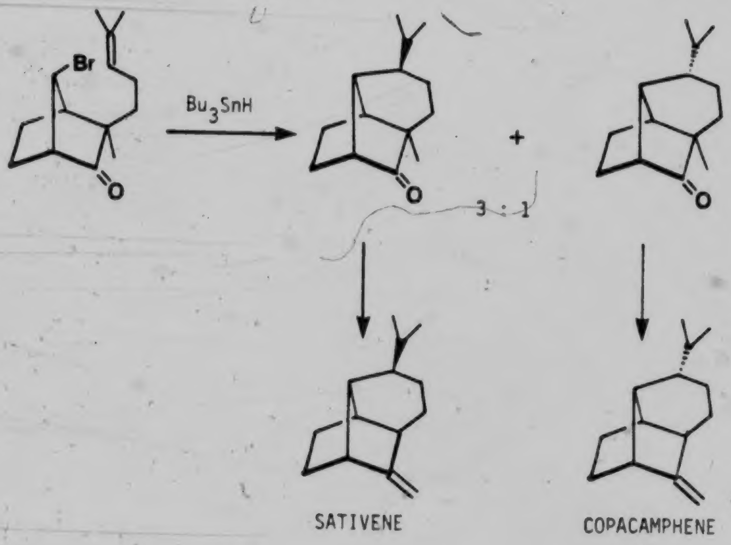
| n | % | RELATIVE[a] % |
|---|---|---|
| 2 | 0 | 100 |
| 3 | 94 | 6 |
| 4 | 71 | 29 |
| 5 | 97 | 3 |

[a] Absolute yields of cycloalkanones were 65–75%. Radicals were generated from carboxylic acids.

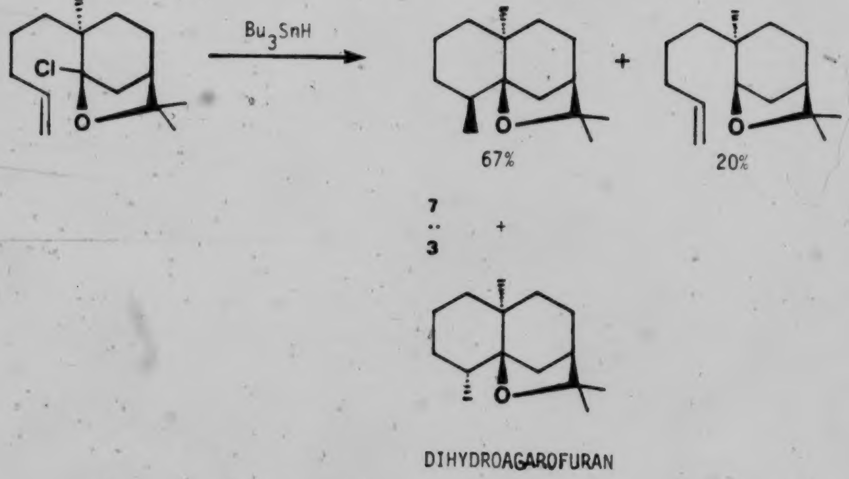
## TABLE 5
## RATE CONSTANTS FOR CYCLIZATION OF RADICALS ONTO VARIOUS FUNCTIONAL GROUPS

| | k 25°C (sec$^{-1}$) | k 80°C (sec$^{-1}$) |
|---|---|---|
| C≡N | $4.0 \times 10^3$ | $4.0 \times 10^4$ |
| C=C | $1.1 \times 10^5$ | $5.3 \times 10^5$ |
| C≡C | | $1.2 \times 10^5$ |

**d) Synthetic methods.** Until three years ago, there were very few examples of the use of intramolecular radical cyclizations in synthetic organic chemistry. Despite the enormous potential of such reactions for the construction of complex carbon frameworks there is only a handful of examples where the methodology was incorporated as the crucial step of a synthesis. The synthesis of sativene and copacamphene[63] (equ 56) and of dihydroagarofuran[64] (equ. 57) are the only examples known to us in which carbocyclic rings are formed from olefinic radicals.


Br
Bu$_3$SnH
O
+
3 : 1
SATIVENE
COPACAMPHENE

(equ 56)


Cl
O
Bu$_3$SnH
+
67%
20%
7 : 3
+
DIHYDROAGAROFURAN

(equ 57)

Due to their regioselectivity, stereoselectivity and efficiency, radical ring closure reactions have become increasingly more attractive as a mean of preparing cyclic compounds. This potential, however, was not realized until two years ago when a large number of publications started to appear on the subject. At that time we had already initiated our research in the area and the second chapter of this thesis deals with our results.[65] The little that was published before our work and what has been done since will first be discussed briefly.

**i) Formation of *heterocycles* by radical closure onto double bonds.** In 1981, an intramolecular radical cyclization was reported[66] in the form of a new strategy for construction of $\beta$–lactam derivatives (Table 6). Exocyclic closure was the preferred route when the olefinic substituent, R, was capable of delocalizing the free spin.[67]

Methods for construction of alkaloid skeletons have also been developed based on the cyclization of $\alpha$–acylamino radicals to indolizidine and pyrrolizidines[68] (Scheme 3). Substitution of the double bond allows control of *exo/endo*– regioselectivity.

**Scheme 3**

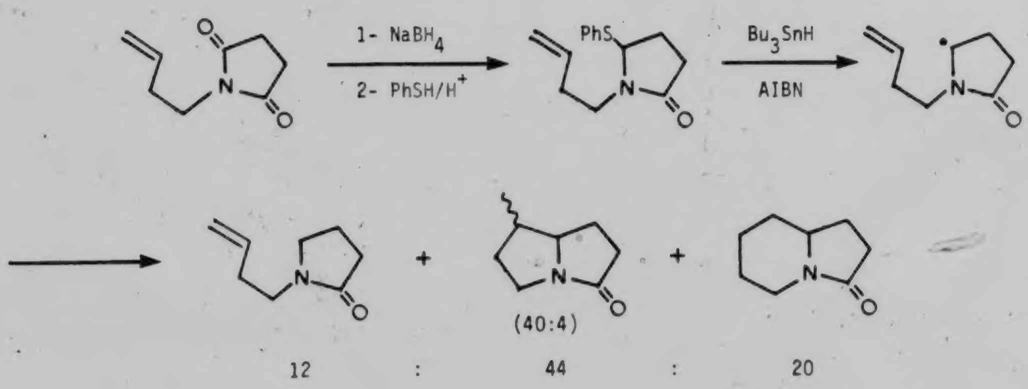
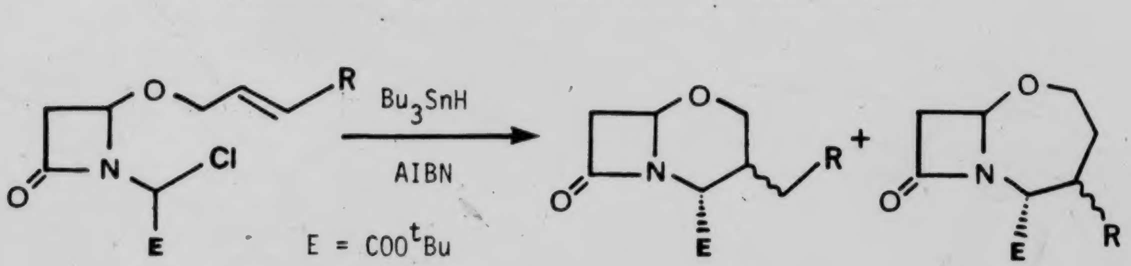
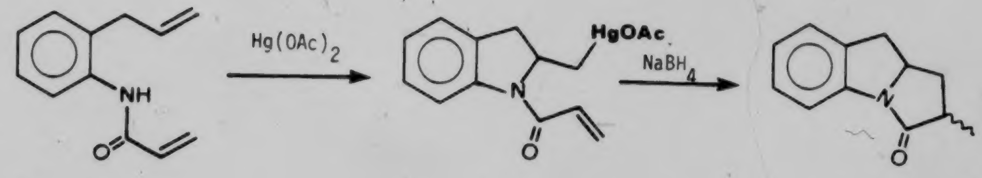


TABLE 6
FORMATION OF $\beta$-LACTAMS BY RADICAL RING CLOSURE


R
O
N
Cl
E
$Bu_3SnH$
AIBN
$E = COO^tBu$
+

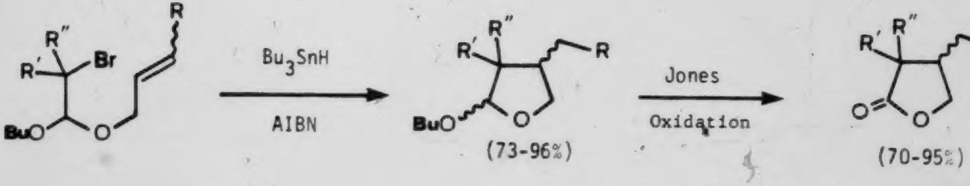
| R | EXO % | ENDO % | YIELD % |
|---|---|---|---|
| H | 0 | 100 | 47 |
| COOMe | 68 | 4 | 72 |
| $CH_2Ph$ | 100 | 0 | 68 |

An intramolecular version of the Giese reaction (see under intermolecular radical additions) leads to structurally related systems via reductive coupling of alkyl mercurials with electron deficient olefins[69] (equ. 58).

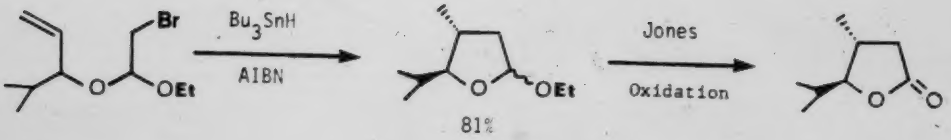

NH
O
$Hg(OAc)_2$
HgOAc
N
$NaBH_4$
N
O

(equ. 58)

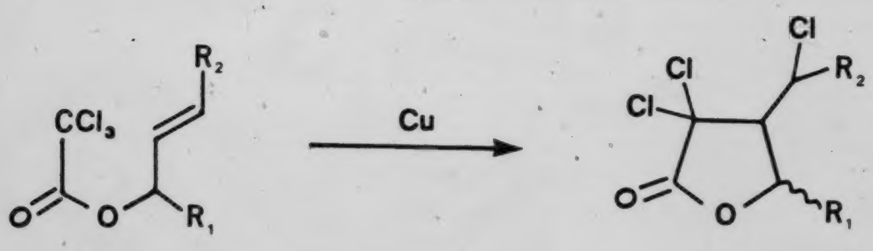
Several procedures have been devised for preparation of $\gamma$–lactones via homolytic cyclizations. Two of them make use of unsaturated bromoacetals[70], [71] (equ. 59, 60) while a third yields trichlorinated $\gamma$–butyrolactones from esters of trichloroacetic acid[72] (equ. 61).


R
R″
R′
Br
BuO
O
Bu3SnH
AIBN
R″
R′
R
BuO
O
(73-96%)
Jones
Oxidation
R″
R′
R
O
O
(70-95%)

(equ. 59)


Br
O
OEt
Bu3SnH
AIBN
O
OEt
81%
Jones
Oxidation
O
O

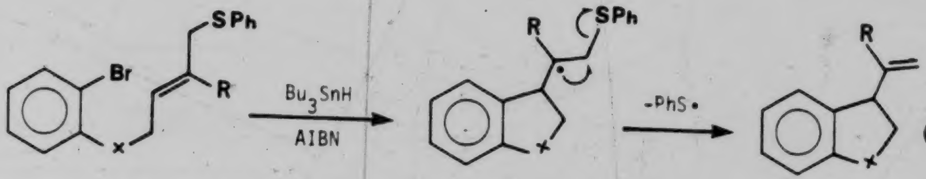
(equ. 60)


R2
CCl3
O
O
R1
Cu
Cl
Cl
Cl
R2
O
O
R1

(equ. 61)

These procedures are useful as they allow for the facile generation of quaternary centers. Such bond formation in polar reactions is strongly affected by steric hindrance and skeletal rearrangements. The high regio– and stereoselectivity observed in most cases permits induction of a new chiral center in the lactones.

We have developed an entirely different approach to the synthesis of $\gamma$-lactones[65] and our results are presented in the next section of this chapter. An interesting approach to the control of regioselectivity in radical cyclizations involves the use of a properly situated leaving group[73] (equ. 62).



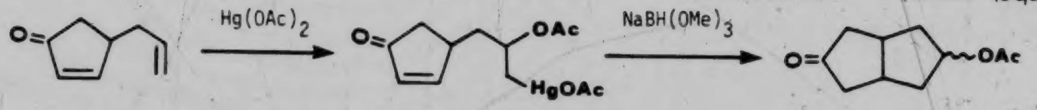
(equ 62)

| | | |
|---|---|---|
| R = H, | X = NH | 96% |
| R = $CH_3$, | X = NH | 56% |
| R = H, | X = O | 75% |

Extrusion of the relatively stable PhS• radical is an extra driving force for exocyclic ring closure.

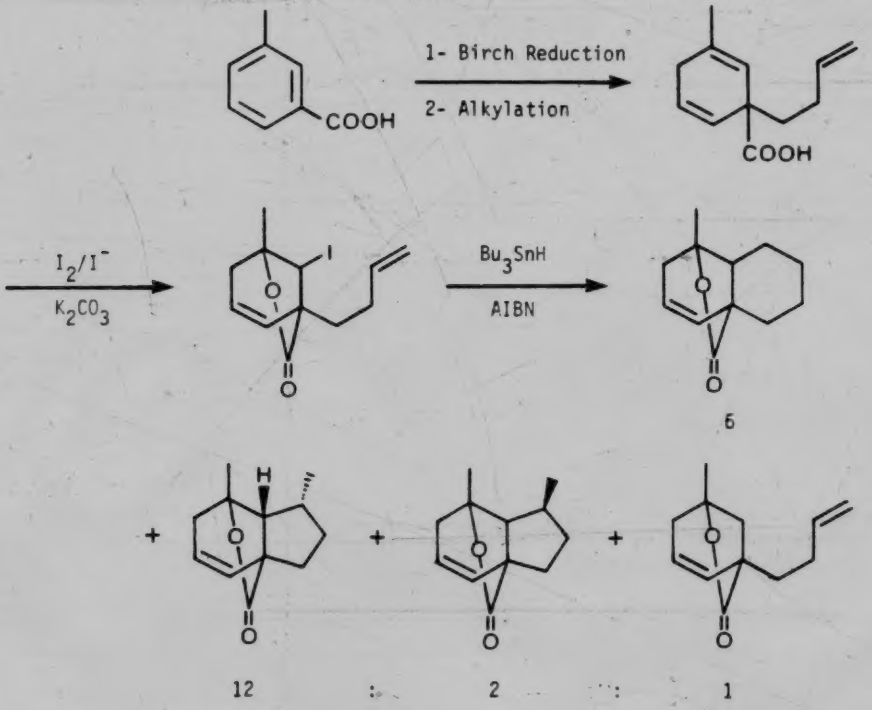
**ii) Formation of *carbocycles* by radical closure onto double bonds.** Enones have been used as substrates, in an intramolecular version of the Giese reaction, to prepare carbocycles[74] (equ. 63). The process is not efficient when quaternary centers are generated. In such cases, reduction without cyclization and reductive elimination back to the alkene are the main processes.

(equ. 63)

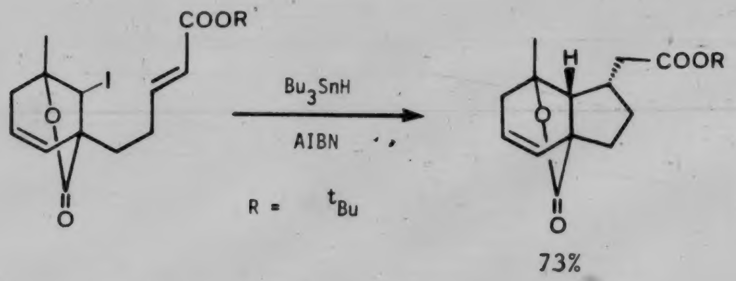

Hg(OAc)$_2$
OAc
HgOAc
NaBH(OMe)$_3$
OAc

Intramolecular radical cyclizations can be used to build structurally complex molecules from relatively simple precursors as exemplified by a new synthetic route to perhydroindanes[75] (Scheme 4).

**Scheme 4**


COOH
1- Birch Reduction
2- Alkylation
COOH
I$_2$/I$^-$
K$_2$CO$_3$
I
O
O
Bu$_3$SnH
AIBN
O
O
6
+
H
O
O
+
O
O
+
O
O
12
:
2
:
1

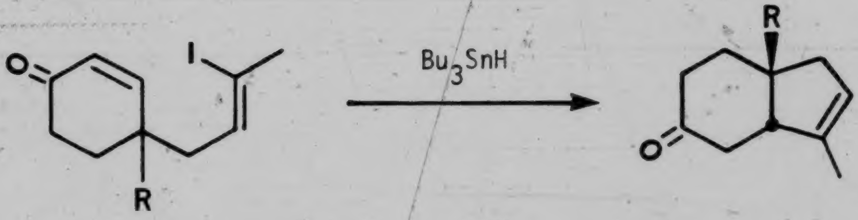
Olefinic substitution allows control over the *exo/endo* cyclization ratio (equ. 64).


COOR
I
O
O
Bu$_3$SnH
AIBN
R = $^t$Bu
H
COOR
O
O
73%

(equ. 64)

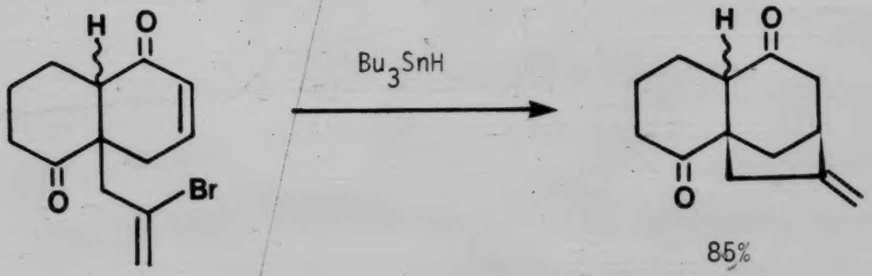
Vinyl radicals can be generated cleanly by tin hydride reduction of vinyl halides. They undergo intramolecular cyclizations to products in which functionality is still present. Substitution of the substrate again allows control of regioselectivity[76] (Table 7). The first entry in Table 7 shows that the reaction is applicable to the generation of quaternary centers.

Intramolecular vinylic radical cyclizations have also been used for preparation of masked 1,4–diketones and giberillic acid skeletons[77] (equ. 65, 66).



(equ. 65)

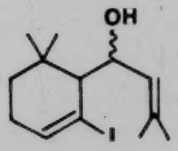
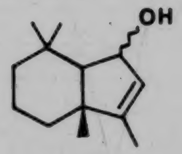
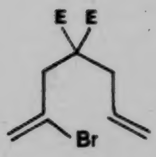
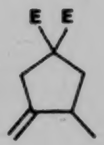
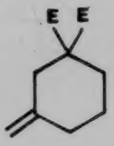
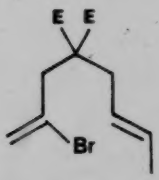
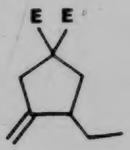
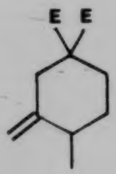
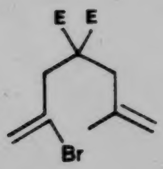
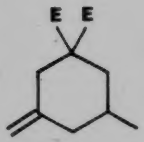
R = H 85%
R = $CH_3$ 83%



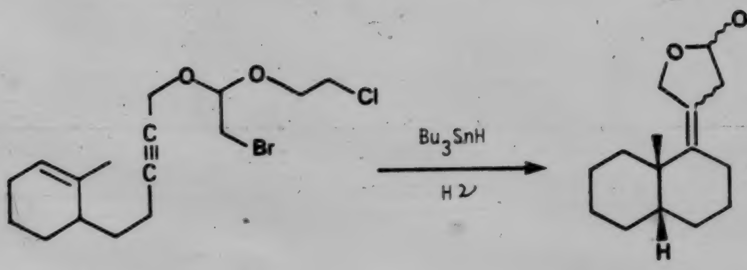
(equ. 66)

**iii) Formation of *heterocycles* by radical closure onto triple bonds.** The cyclization of a bromoacetal onto a triple bond has been used to generate vinyl radicals that were further cyclized onto a double bond[78] (equ. 67).

## TABLE 7
## CYCLIZATION OF VINYL RADICALS

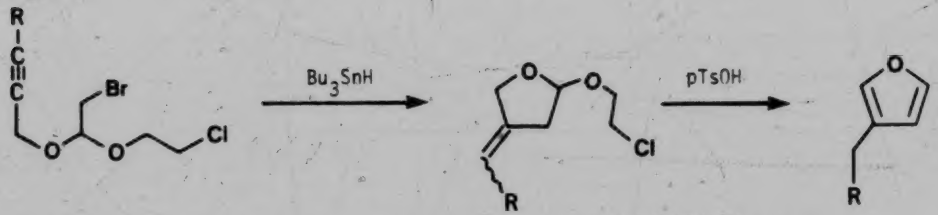
| SUBSTRATES | EXO | | ENDO |
|---|---|---|---|
|  |  | | |
|  |  | 3 : 1 |  |
|  |  | 2 : 1 |  |
|  | | |  |

E = $COOCH_3$


O
O
Cl
C
C
Br
Bu$_3$SnH
H$\nu$
O
O
Cl
H

(equ. 67)

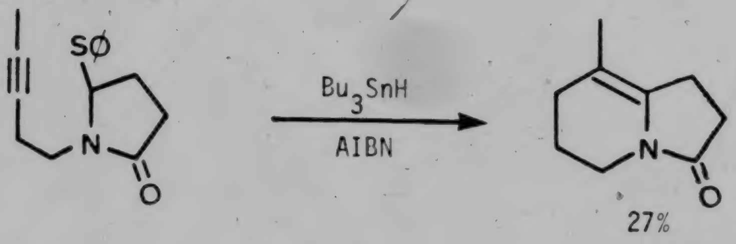
This ring closure reaction has been further developed into a furan synthesis[71] (equ. 68)



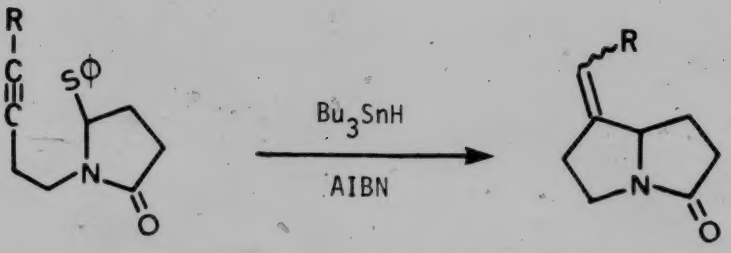
(equ 68)

Easy entry into substituted furans is thus gained.

The reduction of alkyl halides by cobaloxime is known to proceed via electron-transfer[79] and a new route to α-methylene-γ-lactones is based on the cobaloxime induced cyclization of acetylenic ethers[80] (Scheme 5) and acetals[81] (Scheme 6). α-Acylamino radicals undergo radical cyclization onto double bonds (see Scheme 3, p 73). These radicals also undergo closure onto substituted triple bonds[82] (equ.69, 70). The reaction is used to construct alkaloid frameworks.



(equ 69)

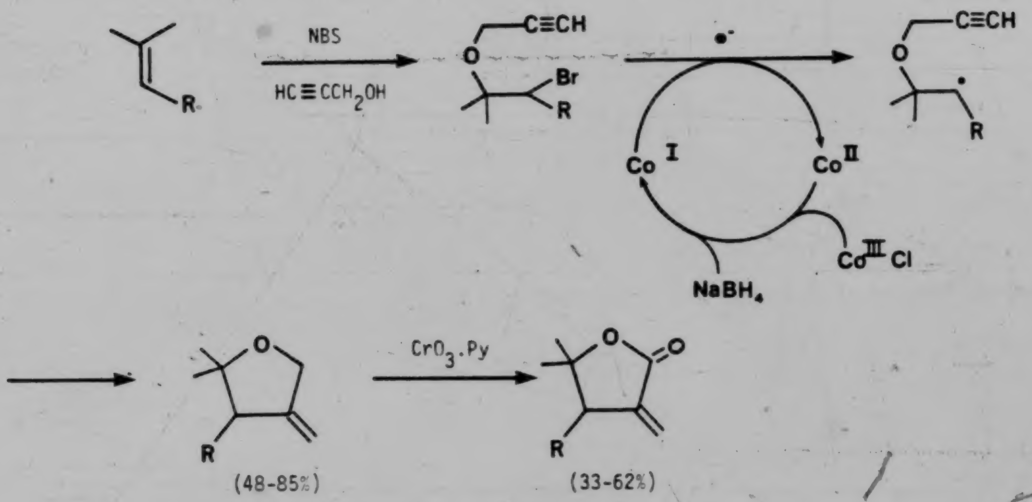


(equ 70)

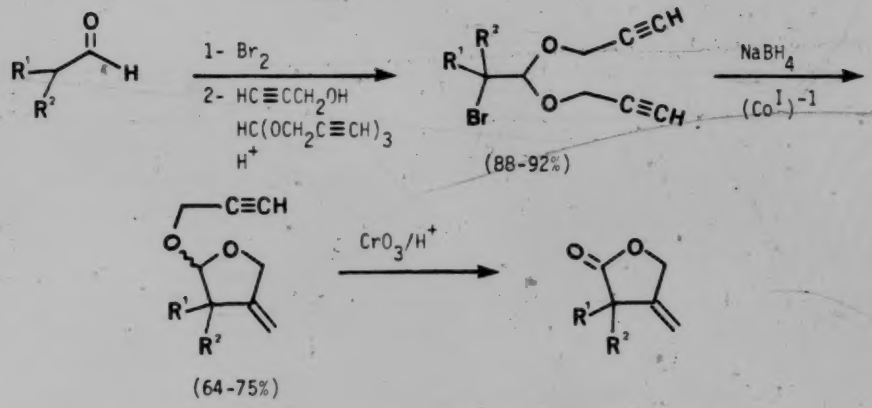
R = $SiMe_3$ 70%

R = $^tBu$ 49%

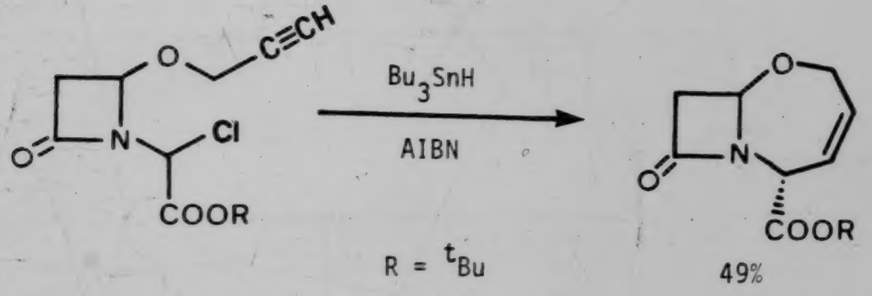
**Scheme 5**


NBS
HC≡CCH2OH
C≡CH
O
Br
R
•⁻
C≡CH
O
R
Co I
Co II
Co III Cl
NaBH4
CrO3.Py
O
R
(48-85%)
O
O
R
(33-62%)

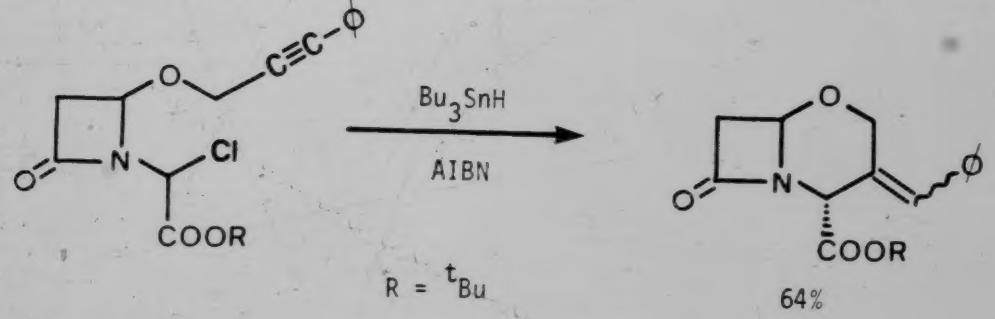
**Scheme 6**


O
R'
R²
H
1- Br2
2- HC≡CCH2OH
HC(OCH2C≡CH)3
H+
R²
R'
Br
O
C≡CH
O
C≡CH
(88-92%)
NaBH4
(CoI)-1
C≡CH
O
O
R'
R²
(64-75%)
CrO3/H+
O
O
R'
R²

The new methodology for the preparation of $\beta$–lactams discussed with respect to Table 6 has been modified by replacing the double bond by a triple bond. This allows entry into 1–oxacephem and 1–oxahomocephem systems. Proper choice of the acetylenic substituent allows control of regioselectivity[63] (equ. 71, 72).

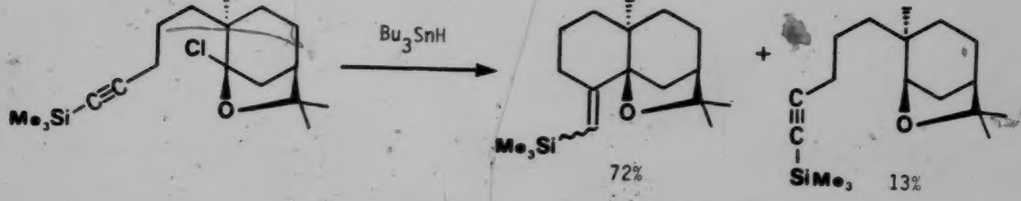

C≡CH
O
N
Cl
COOR
Bu3SnH
AIBN
R = tBu
O
N
COOR
49%

(equ. 71)


C≡C–φ
O
N
Cl
COOR
Bu3SnH
AIBN
R = tBu
O
N
φ
COOR
64%

(equ. 72)

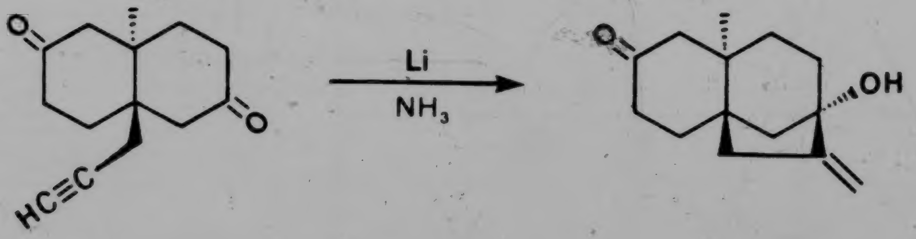
**iv) Formation of *carbocycles* by cyclization onto triple bonds.** The synthetic utility of cyclization of carbon radicals onto carbon–carbon triple bonds for making carbocycles has not been properly appreciated and very few examples are known. (See Buchi's synthesis of $\beta$–agarofuran,[64] equ. 73).


Me3Si
Cl
O
Bu3SnH
O
Me3Si
72%
+
C
C
SiMe3
O
13%

(equ. 73)

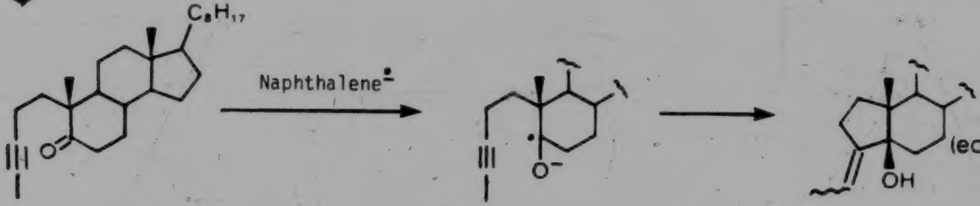
We have developed a general methodology that involves closure of a carbon radical onto a carbon–carbon triple bond and which takes advantage of the fact that ω–hydroxy–acetylene and nitrile compounds are easy to make. This work is described in the discussion section.

**Anion radical closures.** A process that is closely related to the formation of carbocycles described above was first reported by Stork in 1965. It involves lithium–ammonia induced reductive cyclization of δ–acetylenic ketones[84] (equ. 74). The reaction is thought to proceed via radical anions.



(equ. 74)

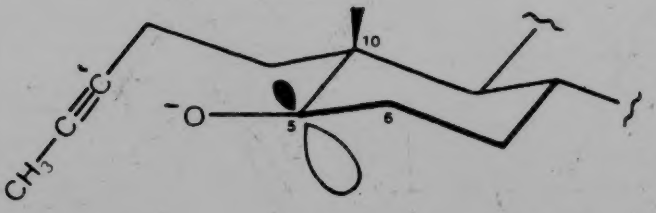
Using naphthalene radical anions, Pradhan and coworkers have undertaken a thorough study of this reaction.[85] The intramolecular radical cyclization of δ–acetylenic and ethylenic–keto–steroids gave 5β–hydroxy steroids via exclusive *exo*–cyclization (equ. 75).



(equ. 75)

The regiospecific formation of *exo*–products was associated with an early transition state. The stereospecificity (only 5β–hydroxysteroids are formed) was regarded as a consequence of preferential axial bond formation by the ketyl radical anion derived from the ketone (Fig. 9).

**Figure 9**

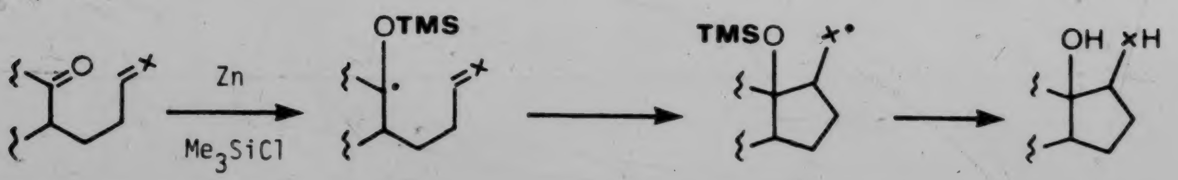


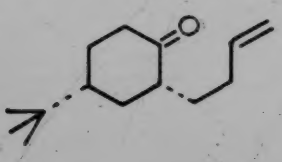
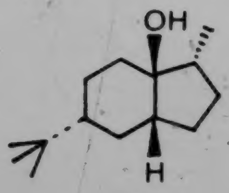
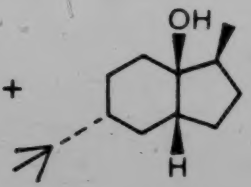
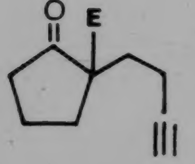
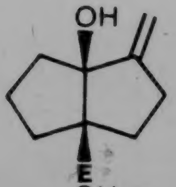
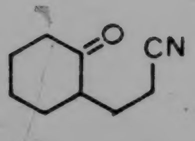
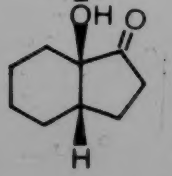
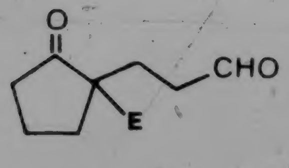
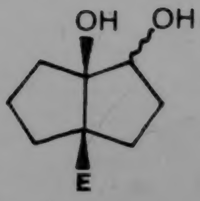
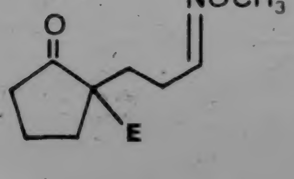
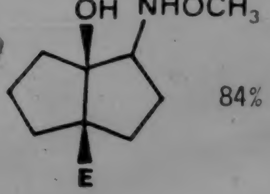
As shown in Figure 9, the semi–occupied molecular orbital (SOMO) at C–5 is unsymmetrically disposed relative to the plane containing C–10, C–5 and C–6. The minimal overlap necessary to reach the transition state is achieved at a longer distance from C–5 in the $\alpha$– direction than in the $\beta$–direction. Hence the preferred formation of 5$\beta$–hydroxysteroids. These authors challenge Beckwith's hypothesis concerning SOMO–LUMO interactions in the radical cyclization of substituted hex–5–enyl radicals. On the basis of theoretical calculations and ionization potentials,[16] they propose a SOMO–HOMO primary interaction. It is claimed that in radical anion attack on substituted $\delta$–ethynyl ketones (for which initial *syn*–attack has been established[15]), the angle of approach necessary[17] for nucleophilic attack on the triple bond based on SOMO–LUMO interactions is impossible. Thus only SOMO–HOMO interactions can come into play.

Along the same lines, Corey has developed a new five–membered ring annulation.[18] It involves treatment of ketones with zinc–chlorotrimethylsilane. This combination is assumed to generate a radical that then undergoes cyclization onto an unsaturated appendage (Table 8). The reaction tolerates a variety of functional groups. It is not definitely proven that the mechanism involves $\dot{\mathrm{C}}$–OSiMe$_3$ radicals rather than $\overset{-}{\mathrm{C}}$–OSiMe$_3$ anions.

## TABLE 8

## Zn/Me$_3$SiCl INDUCED CYCLIZATION OF KETONES


Zn
Me$_3$SiCl
OTMS
TMSO
OH xH

| SUBSTRATES | PRODUCTS<br>YIELD % |
|---|---|
|  |  66% +  7% |
|  |  77% |
|  |  78% |
|  |  75% |
|  |  84% |

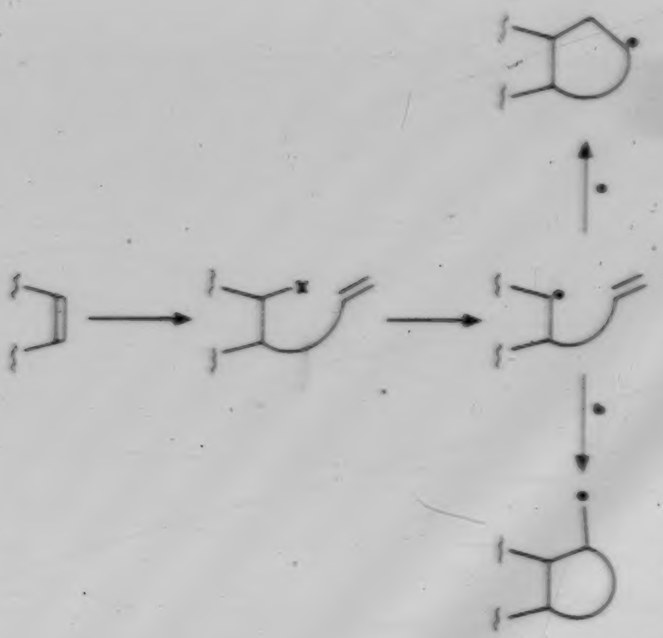
# II. RESULTS AND DISCUSSION

## A. Introduction

As part of an ongoing research program aimed at the development of new methods for making carbon—carbon bonds.[illegible] it was thought that radical ring closure reactions could provide a unique route to cyclic compounds. For a process of this type to be of synthetic value, readily available materials have to be used as substrates. For that reason we focussed our initial efforts on ways of elaborating alkenes into compounds suitable for radical cyclization.

In order to carry out a radical closure, one must generate a radical site in the presence of a pendant group that contains suitably located unsaturation, such as a double or a triple bond. The original concept was to take an olefin, and by means of well established technology, attach to it two units (Scheme 7). One of the units is a group X that would have to be chosen such that the bond between carbon and X can be broken in a homolytic fashion. The second unit is a pendant group containing a properly positioned multiple bond.

Scheme 7



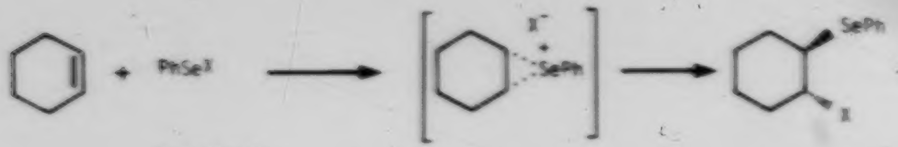
## B. Carbon–Carbon Bond Formation by Radical Ring Closure of β-(Phenylselenol)esters: A New Method for the Preparation of γ-Lactones

**a) Preparation of β-(phenylselenol)esters:** Because of our experience with selenium chemistry, we examined the possibility of using the phenylseleno moiety as a potential X group in Scheme 7. It was known that the carbon–selenium bond can be broken very easily with tin radicals generated by the AIBN-initiated thermal decomposition of triphenyltin hydride.[81] This radical chain-reaction affords alkyl radicals cleanly and efficiently (Scheme 8) and has become the method of choice for the reductive removal of selenium from organic molecules.[82]

**Scheme 8**

$$\begin{array}{llr}
Ph_3SnH \xrightarrow[\Delta]{AIBN} Ph_3Sn\bullet + H\bullet & & \text{Initiation} \\
R-SePh + Ph_3Sn\bullet \longrightarrow R\bullet + Ph_3Sn-SePh & & \\
 & & \text{Propagation} \\
R\bullet + Ph_3SnH \longrightarrow RH + Ph_3Sn\bullet & &
\end{array}$$

Most methods for the addition of a phenylseleno group to a double bond involve electrophilic ionic addition of PhSeX (where X is Cl, Br) to the alkene. The reaction proceeds via episelenium ions and gives *trans*-adducts[83] (equ 75).

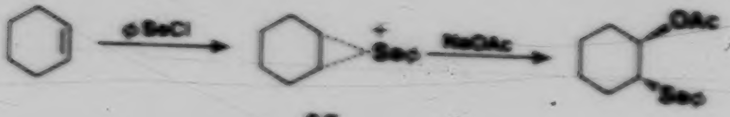


X = Cl, Br

25

(equ 75)

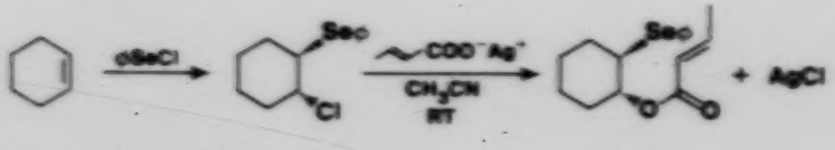
If a nucleophile is present, it can sometimes be incorporated into the final product (equ 76).



**25**

(equ 76)

Nucleophiles that have been successfully employed include acetate,[91] trifluoroacetate,[91] azide ions,[90] and methanol.[91] On the basis of these known reactions, we set out to attach an unsaturated ester unit and a phenylseleno group to a double bond as described in equation 77.



**26**

(equ 77)

Two factors had to be taken into consideration before the methodology of equ 77 was adopted. First, the addition of benzeneselenenyl chloride across a double bond is a reversible process.[91] Therefore, the unsaturation present in the pendant group had to be deactivated to prevent reaction with benzeneselenenyl chloride. $\alpha,\beta$–Unsaturated esters satisfied this requirement and in no cases could we detect any products derived from addition of the electrophile to the double bond of the ester.

Secondly, in order to introduce an ester unit in a $\beta$–position with respect to the phenylseleno group, an (*E*)–2–butenoate entity that was nucleophilic enough to react with adduct **25** was necessary. To this end, the benzeneselenenyl chloride adduct of cyclohexene was treated with (*E*)−2−butenoic acid and several of its salts (Table 9).

It is apparent that both (*E*)−2−butenoic acid and its sodium salt were ineffective for producing ester **26**. The thallium salt provided some of the desired material in modest yield, but silver (*E*)−2−butenoate proved to be the reagent of choice.

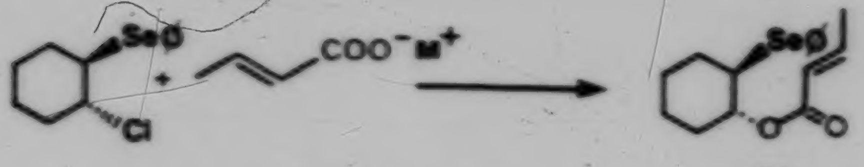
The experimental procedure for making β−(phenylselenol)esters consists of adding a given alkene to a dichloromethane solution of benzeneselenenyl chloride. Formation of the corresponding *trans*− adduct is easily observed by disappearance of the orange color that is characteristic of selenenyl halides. The adduct is not isolated but the solution is diluted with dry acetonitrile and silver (*E*)−2−butenoate is added. Because of the two−phase nature of this reaction, the use of a sonic bath for mixing led to improved yields over conventional magnetic stirring. Of course, the experiments have to be carried out with protection from light in order to prevent decomposition of the silver salt. Simple filtration and chromatography affords the desired esters. A number of these preparations were carried out and the results are shown in Table 10. The Table reveals that yields of β−(phenylselenol)esters are generally good. The reaction is not limited to (*E*)−2−butenoic acid. Entries 8 and 9 show that silver propenoate can be used and the corresponding esters are obtained with comparable ease. Also included in Table 10 (entry 10) is the preparation of an iodoester according to the literature procedure.[illegible] It was made in order to compare the ring closure of an iodide with that of a selenide.

All of our β− (phenylselenol)esters have clean *trans*−stereochemistry as expected from literature[illegible] analogy.* The *trans*−stereochemistry for most of the adducts in Table 10 was derived from the coupling constant between the −CH−SePh and the −CH−OOC protons. In each case, its value was greater than 7 Hz.

---

*The structure of adducts and the *trans*−stereochemistry were derived from $^1$H NMR analysis. Among the features present in the $^1$H NMR spectra were resonances at δ 1.85 (dd, J = 10.0,2.0 Hz, 3H), 5.8(dq, J = 16, 2 Hz, 1H) and 6.9 (dq, J = 16, 7 Hz, 1H) characteristic of the (*E*)−2−butenoic segment, −OC−CH=CHCH$_3$. The proton attached to the carbon bearing the selenium atom, −CH−SePh, resonated at δ 3.10−3.70 ppm depending on the structure of the starting olefin. This range is in agreement with values reported for β−(phenylselenol) esters of acetic acid.[illegible] Similarly, the proton attached to the carbon bearing the ester functionality, −CH−OCO−, was observed at δ 4.3−5.2 ppm.[illegible] The vinylic protons of propenoate esters **33**, **34**, Table 10), −O−C−CH=CH$_2$, had characteristic resonances at δ 5.75 (dd, J = 10, 2 Hz, 1H), 6.00 (dd, J = 17, 10 Hz, 1H), and 6.30 (dd, J = 17, 2Hz, 1H).

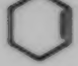
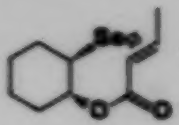
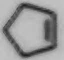
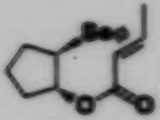
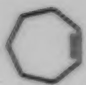
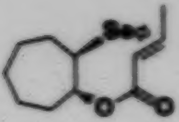
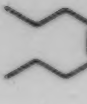
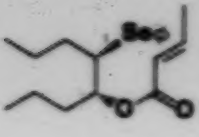
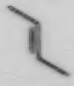
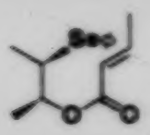
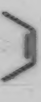
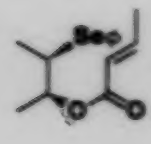
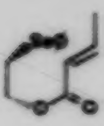
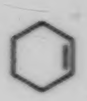
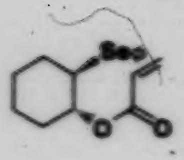
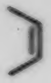
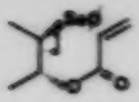
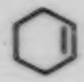
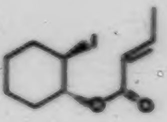
## TABLE 9
## PREPARATION OF β-(PHENYLSELENO) ESTERS USING VARIOUS SALTS OF CARBOXYLIC ACIDS


SeØ
Cl
+
COO⁻M⁺
SeØ
O
O

**26**

| M⁺ | ESTER % |
|---|---|
| H | 0 |
| Na | 0 |
| Tl | 51.6 |
| Ag | 77.3 |

### TABLE 10
### PREPARATION OF β-(PHENYLSELENO) ESTERS

| | Alkene | β-phenylselenoester | | % Yield |
|---|---|---|---|---|
| 1 |  |  | 26 | 77 |
| 2 |  |  | 27 | 74 |
| 3 |  |  | 28 | 76 |
| 4 |  |  | 29 | 92 |
| 5 |  |  | 30 | 88 |
| 6 |  |  | 31 | 75 |
| 7 | |  | 32 | 48 |
| 8 |  |  | 33 | 67 |
| 9 |  |  | 34 | 76 |
| 10 |  |  | 35 | 94 |

With a preparation of the β-(phenylseleno)esters available we were now ready to study the generation of the radical site by homolysis of the carbon–selenium bond and to examine conditions for the cyclization.

**b) Cyclization of β-(phenylseleno)esters:** Treatment of β-(phenylseleno)esters such as **26** with triphenyltin hydride in the presence of an initiator (AIBN) was expected to cause homolysis of the carbon–selenium bond and produce radical **36** (Scheme 9), which we hoped would undergo ring closure via *exo*– or *endo*–attack (path a and b respectively) followed by rapid hydrogen transfer by triphenyltin hydride to give γ-lactones **37** or δ-lactones **38**. In the event, when a dilute benzene solution of β-(phenylseleno)ester **26** (ca. 0.02 M) was treated simultaneously with benzene solutions of a catalytic amount of AIBN and a small excess (1.1 – 1.2 equivalents) or triphenyltin hydride, radical **36** was generated cleanly and underwent exclusive closure to the 5-membered lactones **37**. Isomeric δ-lactones **38** and ester **39** (product of hydrogen transfer to radical **36**) could not be detected in the reaction mixture (TLC, VPC, $^1$H NMR, $^{13}$C NMR). The absence of ester **39** is a consequence of the experimental procedure that was designed for these cyclizations. Use of dilute substrate solutions (0.02 M) and slow addition of the reagents over 15 h by means of a syringe pump ensured that no exess of triphenyltin hydride was present in the reaction mixture. Both factors maximize the extent of cyclization of radical **36** prior to hydrogen transfer. The presence of a radical initiator was found to be essential. Use of a higher temperature (through use of toluene as solvent) resulted in a decrease in the yield of cyclized products. Extrusion of (*E*)-2-butenoyl radicals from **36** (i.e. β-fission) was not observed (Scheme 9). Experiments of this sort were carried out on all substrates of Table 10 and the results are shown in Table 11.

Examination of Table 11 reveals that all β-(phenylsenelo)esters (**26** – **34**) and iodo ester **35** underwent exclusive *exo*-ring closure to mixtures of γ-lactones. Yields were generally 60–80% except for propenoate esters (**33**, **34**) which gave poor results.

**c) Identification of γ-lactones from β-(phenylseleno)ester cyclizations.** Scheme 9 showed that two sets of products can arise, at least in principle, from cyclization of radical **36**: γ-lactones from exocyclic closure and δ-lactones from the

### Scheme 9

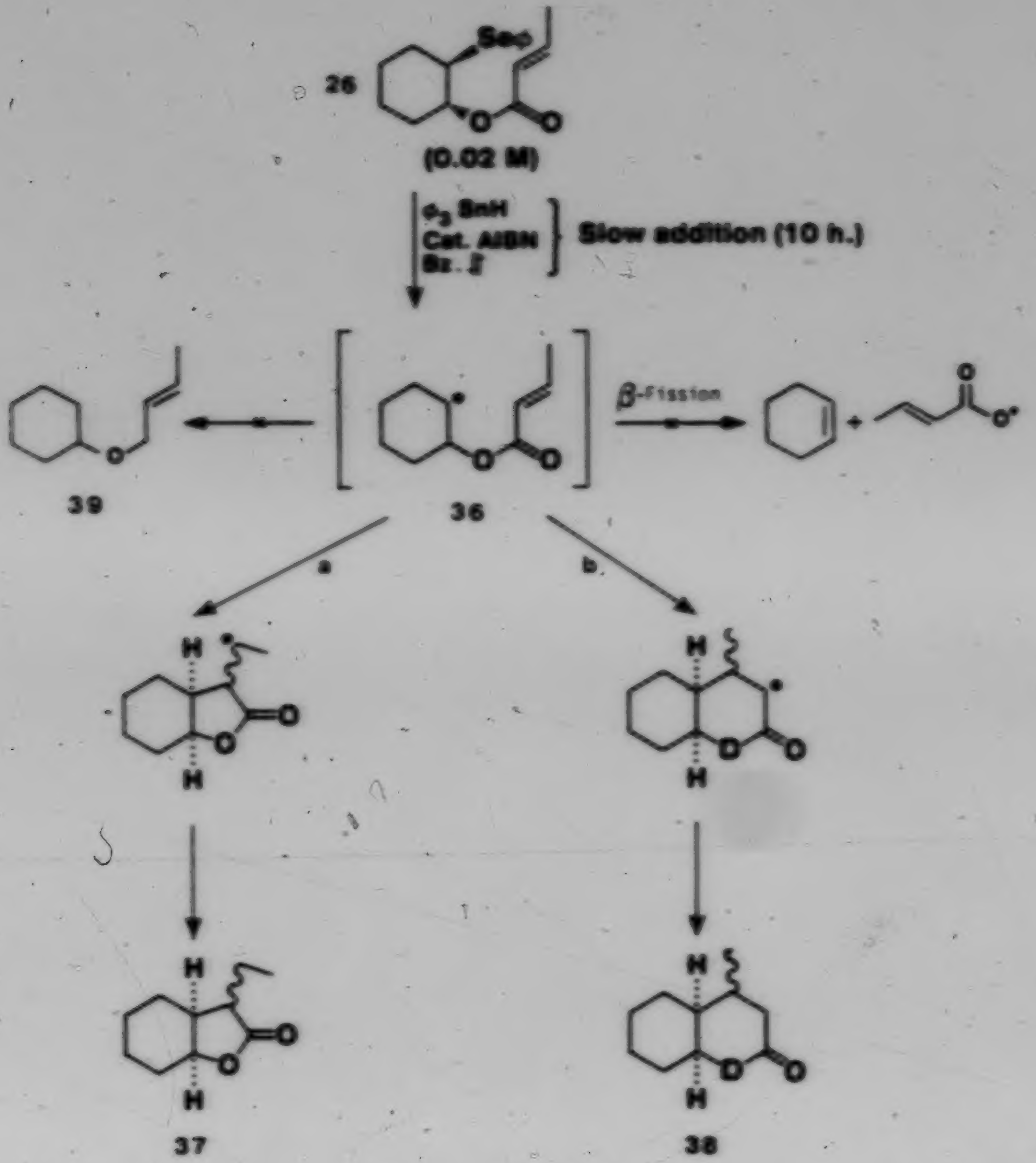
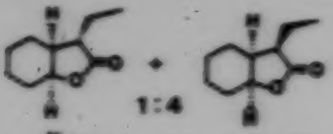
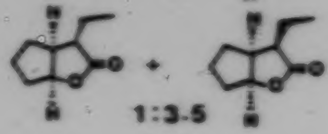
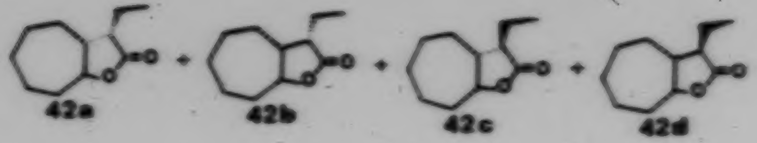
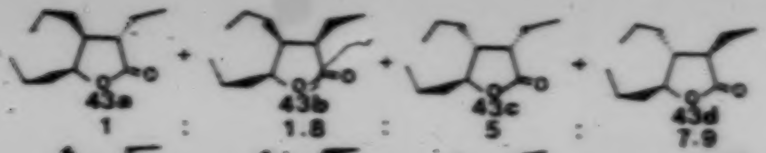
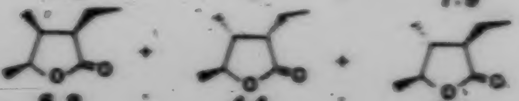
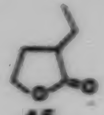
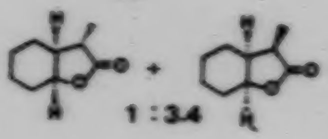
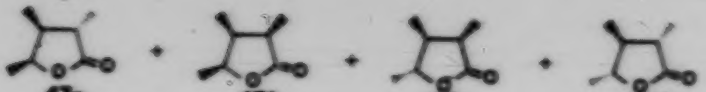

26
Seφ
O
O
(0.02 M)
φ$_3$ SnH
Cat. AIBN
Bz. Δ
Slow addition (10 h.)
β-Fission
O•
39
36
a
b
H
H
O
O
D
37
38

TABLE II
CYCLIZATION OF β-(PHENYLSELENO) ESTERS

| β-phenylselenoester | γ-lactones[b,c] | % Yield[a] |
|---|---|---|
| 26<br>35[d] | **40a**  **40b**<br>1:4 | 85<br>56 |
| 27 | **41a**  **41b**<br>1:3.5 | 61 |
| 28 |  **42a** + **42b** + **42c** + **42d** | 65 |
| 29 |  **43a** : **43b** : **43c** : **43d**<br>1 : 1.8 : 5 : 7.9 | 77 |
| 30<br>31 |  1 : 6.8 : 4.4 : 7.9<br>1 : 5.5 : 4 : 7.3<br>**44a** **44b** **44c** **44d** | 66<br>67 |
| 32 |  **45** | 17 |
| 33 | **46a**  **46b**<br>1 : 3.4 | 24 |
| 34 |  **47a** + **47b** + **47c** + **47d**<br>1 : 6.6 : 5 : 7.4 | 25 |

[a] Yields refer to isolated products of analytical purity.

[b] Ratios determined by ¹H NMR (400 MHz) by integration of –CH–OCO resonances.

[c] See text for evidence to support stereochemical assignments.

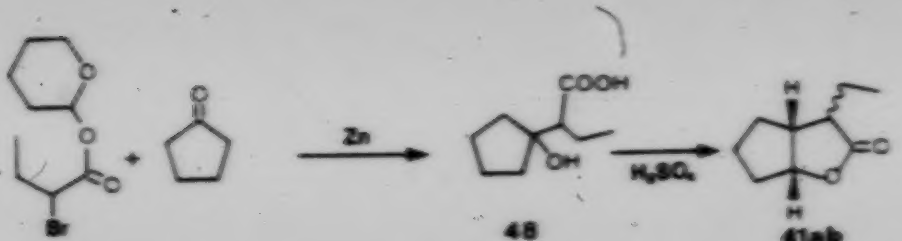
[d] Iodoester.

endo-pathway

The two classes can be differentiated easily by their infrared absorption. γ-lactones typically absorb at 1760 – 1770 $cm^{-1}$ whereas the δ-lactone carbonyl gives a band near 1730 $cm^{-1}$. Our cyclization products absorb at 1760 – 1770 $cm^{-1}$, and are clearly γ-lactones.

The relative stereochemical relation between the substituents around the periphery of the 5-membered ring was more difficult to establish. Only lactones **45**,[illegible] **46**[illegible] and **47**[illegible] were known compounds. In each case, the spectral characteristics of our materials were very close to those reported in the literatuare (see Experimental Section).

In the case of lactones **41a** and **41b**, authentic samples were prepared[illegible] (equ. 78) and found to be identical with the products of the cycliation of ester **27**.



**48**

**41ab**

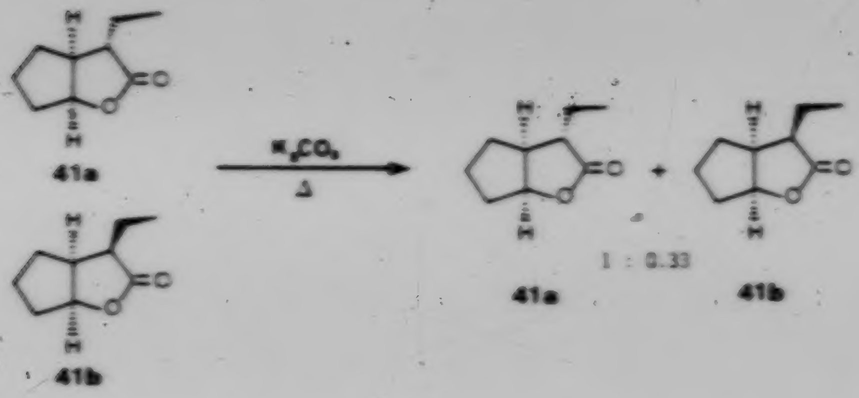
(equ. 78)

Lactones **40**, **42**, **43** and **44** were identified by comparison of their spectral characteristics with those of structurally related compounds and will be dealt with separately.

Lactones **40**, **41** and **46** were all *cis*-fused and were mixtures of *exo*- and *endo*-isomers (Table 11). The ring fusion geometry was determined by $^1$HNMR (400 MHz). In *cis*- 2-oxabicyclo(4.3.0)nonan-3-one systems, the $^1$HNMR signal of –CH–O occurs at δ 4.3 – 4.65.[illegible] For *trans*-ring fusion the signal is at δ 3.60–3.78[illegible] (Table 12). For *cis*-fused 2-oxabicyclo[3.3.0]octan-2-one, the corresponding signal is at δ 5.0.[illegible] (The formation of a *trans*-ring fused 2-oxabicyclo[3.3.0]octan-2-one is very difficult to achieve.[illegible] Examination of Table 12 reveals that lactones **40**, **41** and **46** all exhibit chemical shifts characteristic of *cis*–ring fusion.

The stereochemistry at C–3 (i.e. *exo*/*endo* ratio) in lactones **40ab** (Table 11) was established by spectral comparison with the published[illegible] $^1H$ NMR data on **46ab**.

Differentiation between *exo*– and *endo*–isomers **41a** and **41b** (Table 11) was made on the basis of $^{13}C$ NMR measurements and equilibration experiments on authentic samples of the individual components[illegible] obtained by preparative VPC (see Experimental Section). When lactones **41a** or **41b** were refluxed in tetralin in the presence of anhydrous potassium hydrogen carbonate, isomerization occurred to an equilibrium mixture containing **41a** and **41b** in a ratio (VPC) of 1:0.33 (equ 79).



(equ 79)

The thermodynamically more stable product was assigned structure **41a** (*exo*–stereochemistry) on the basis of a non–bonded interaction present in the *endo*–isomer (Figure 10). Further support for the assignment is found in the $^{13}C$ NMR spectra of the individual isomers. For *exo*–compound **41a** the sum of $^{13}C$ chemical shifts of the methylene carbons should be higher than in the corresponding *endo*–isomer **41b**.[illegible] The observed values for $\Sigma_{\alpha C}$ are 116.0 ppm and 102.5 ppm for **41a** and **41b**, respectively, in agreement with the assignment.

Radical cyclization of $\beta$–(phenylseleno)esters **30** and **31** [derived from (*E*) and (*Z*)–2–butene, respectively)] afforded a mixture of four isomeric lactones **44a–d** in almost identical ratios. The stereochemistries shown in Table 11 were assigned, tentatively, by

## TABLE 12
## CHEMICAL SHIFT OF THE $-CH-O\overset{O}{C}-O$ PROTON OF LACTONES

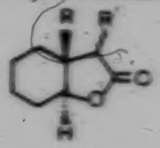
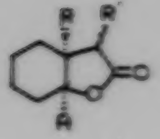
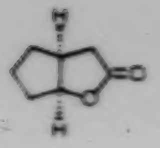
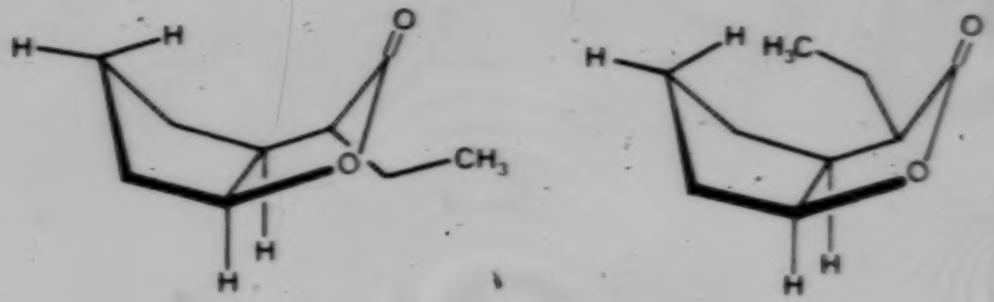
| Lactone | $-CH-O\overset{O}{C}-$ resonance<br>ppm |
|---|---|
|  | 3.60 – 3.78[illegible],[illegible] |
|  | 4.3 – 4.65[illegible] |
|  | 5.00[illegible] |
| **40a** | 4.37 |
| **40b** | 4.49 |
| **41a** | 4.94 |
| **41b** | 4.86 |
| **46a** | 4.42 |
| **46b** | 4.52 |
| **42a** | 4.23 |
| **42b** | 4.55 |
| **42c** | 4.09 |
| **42d** | 4.58 |

Figure 10



EXO **41a**

More Stable

ENDO **41b**

Less Stable

comparison with published[illegible] detailed $^1$H NMR data on the four isomeric 2,3,4-trimethylbutyrolactones **47a–d**. Similarly, lactones **43a–d** were tentatively assigned the stereochemistries shown (Table 11) by comparison with lactones **44a–d** and **47a–d**.

Cyclization of $\beta$-(phenylseleno)ester **28** gave a mixture of four isomeric bicyclic lactones **42a–d** (Table 11). By analogy with lactones **40**, **41** and **46**, the $^1$H NMR chemical shift of –CH–O (Table 12) was used to determine the stereochemistry at the ring junction. Isomers **42a** and **42c** having resonances at higher field than **42b** and **42d**, were assigned a *trans*–ring fusion geometry and the latter pair a *cis*–geometry. The stereochemistry at C–3 was tentatively assigned by comparison with lactones **43**, **44** and **47**.

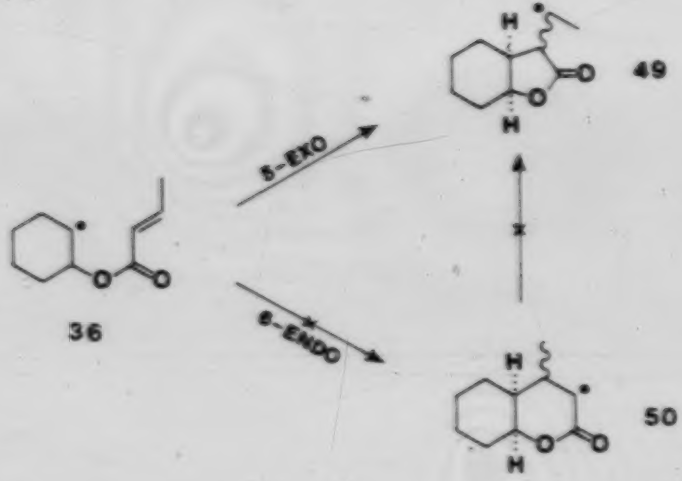
Ester **32** cyclized to a single lactonic product **45**, whose structure was evident from IR, $^1$H NMR and $^{13}$C NMR measurements.

**d) Theoretical aspects:**

*i) Regiochemical outcome*. Radicals structurally related to the 5–hexenyl radical can undergo ring closure via two different modes as depicted in Scheme 10. *Exo*–closure leads to the formation of a five–membered lactone whereas *endo*–cyclization gives a 6–membered lactone. Both processes are allowed by the Baldwin rules[illegible]. All experiments listed in Table 11 give exclusive 5–*exo*–ring closure.

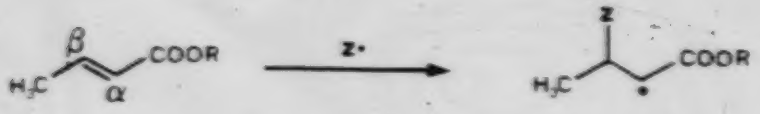
We established that radical **49** is not formed under equilibrium conditions by isomerization of radical **50**. To prove this point, $\alpha$–(phenylseleno)lactone **51** (p. 100) was

**Scheme 10**



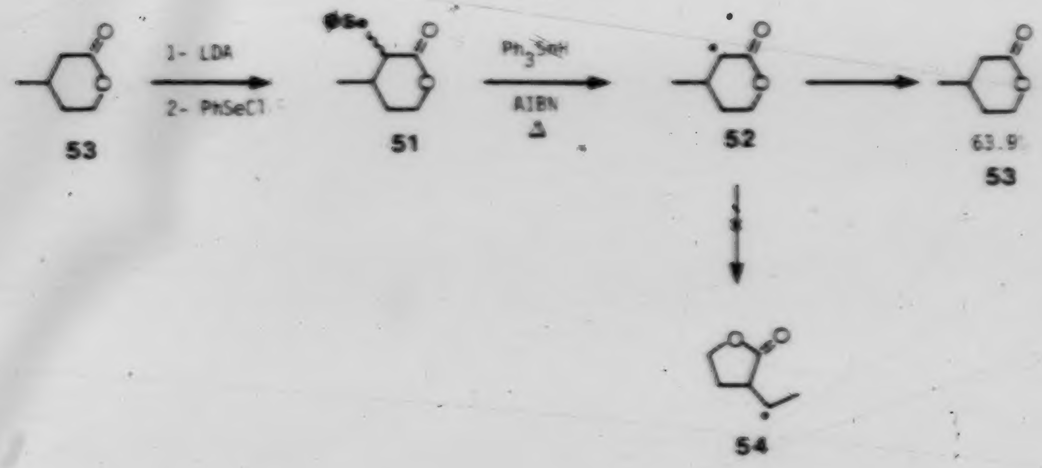
prepared and reduced with triphenyltin hydride, under conditions identical to those used for radical cyclizations. Radical **52** was generated cleanly and it led to lactone **53** without rearrangement to **54** (Scheme 11). This result implies that *exo*–closure of radical **36** (Scheme 10) is kinetically controlled and does not result from thermodynamic equilibrium between *exo*– and *endo*–radicals (**49** and **50** respectively).

The regiospecific intramolecular attack of the radical at the $\alpha$–position of the $\alpha,\beta$–unsaturated ester is, in some respects, unusual. It contrasts with *intermolecular* radical additions to (*E*)–2–butenoate esters which are known to proceed almost exclusively at the $\beta$–position[16a] (equ. 80).



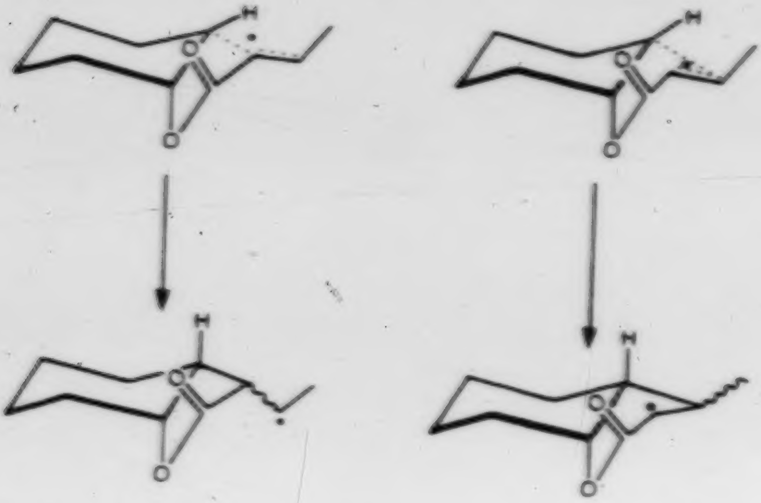
(equ. 80)

**Scheme 11**



Like the 5–hexenyl radical 3 (p.47), the present reaction shows a reversal of the regiochemistry associated with corresponding intermolecular processes. Resonance stabilization of radicals such as 50 (Scheme 10) by delocalization through electron withdrawing groups is not very important[4] because the transition state occurs at an early stage along the reaction coordinate. Therefore such delocalization should not provide a significant driving force for *endo*–cyclization. The factors responsible for the *exo*–preference in radical closure of the 5–hexenyl radical 3 must also operate in the present case. The kinetic preference for formation of 5–membered rings is probably a consequence of stereoelectronic control in the transition state.[34,34,107] According to this hypothesis, attack of a radical on a double bond follows the pathway shown in Fig. 5, and this preferred pathway is more readily accommodated by the transition state leading to exocyclic products (Fig. 11).

**Figure 11**



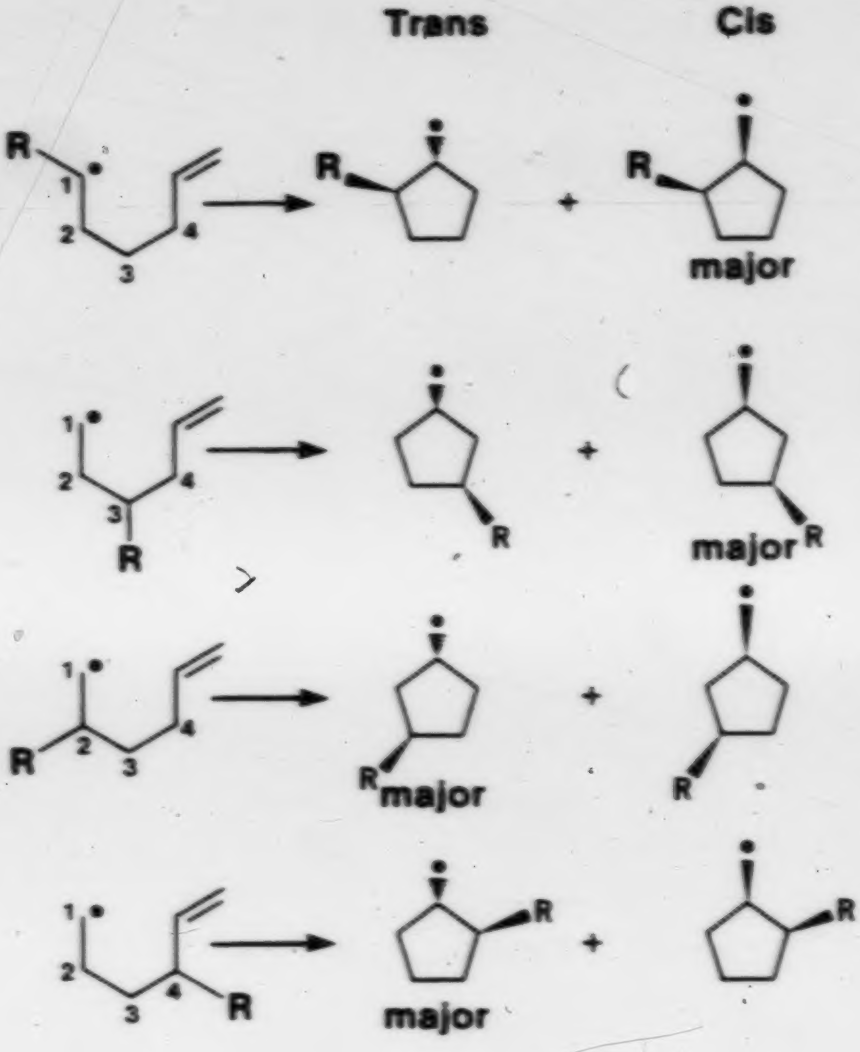
EXO

ENDO

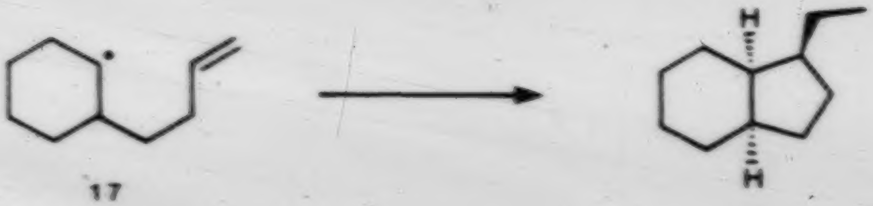
*iii) Relative stereochemistry of peripheral substituents:* Beckwith proposed guidelines to help predict the relative stereochemistry of substituents in products derived from cyclization of substituted 5–hexenyl radicals.[34] They are summarized again for convenience in Figure 12. The information in Fig. 12 reveals that C–1 and C–3 substituted 5–hexenyl radicals give predominantly *cis*–disubstituted cyclopentanes whereas C–2 and C–4 substituted 5–hexenyl radicals favour the formation of *trans*–disubstituted products.

The 2–(but–3–enyl)cyclohexyl radical 17 (p. 66) is formally a 1,2–disubstituted radical. The theory of stereoelectronic control was used to explain the preferred

Figure 12


Trans
Cis
R
1
2
3
4
major
R
major
R
major
R
major

formation of product **18**[34] (equ. 47). This is shown again as equ. 81.



**17** **18** (equ. 81)

The formation of **18** was considered to be favoured by a better overlap of the semi-occupied *p* orbital and the antibonding $\pi^*$ orbital in a transition state conformation in which the substituent is in an axial position (Fig. 8, p. 67).[34]

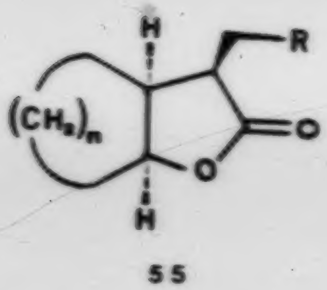
The same arguments can be used to justify the formation of the major products in the cyclization of radicals derived from esters **26**, **27**, **28**, **33** and **35**, all of which can be considered as 1,2-disubstituted 5-hexenyl radicals. Examination of Table 11 reveals that in all cases, the favoured lactone has the relative stereochemistry indicated in Fig. 13 (p. 104).

The preferred transition state conformations involved in 5-*exo* cyclization of radicals such as **26**, **27**,**28**, **33** and **35** are depicted in Fig. 14 (p. 104).

Inspection of models shows that the required transition state for *exo*-cyclization (Fig. 5, p. 60) is more readily attained in the conformation leading to product **55** and hence, the relative stereochemistry of the three asymmetric centers of the major isomer corresponds to that observed in carbocyclic systems.[34] As pointed out by Beckwith,[34] the departure from the guidelines in the case of radical **17** is attributable to additional constraints imposed by the presence of a ring.

The radicals derived from esters **29**, **30**, **31** and **34** (Table 11) are 1,2-disubstituted acyclic 5-hexenyl radicals. Therefore, they should conform to the guidelines according to which the major product should be **57** where the new substitutent resulting from cyclization is disposed *cis* to the formal C-1 substituent and *trans* to the C-2 substituent. Conversely, the minor isomer should have the relative configuration **58** (Fig. 15). Also shown in Fig. 15 are the major, **59** and minor, **60** isomers observed in our cyclization

Figure 13

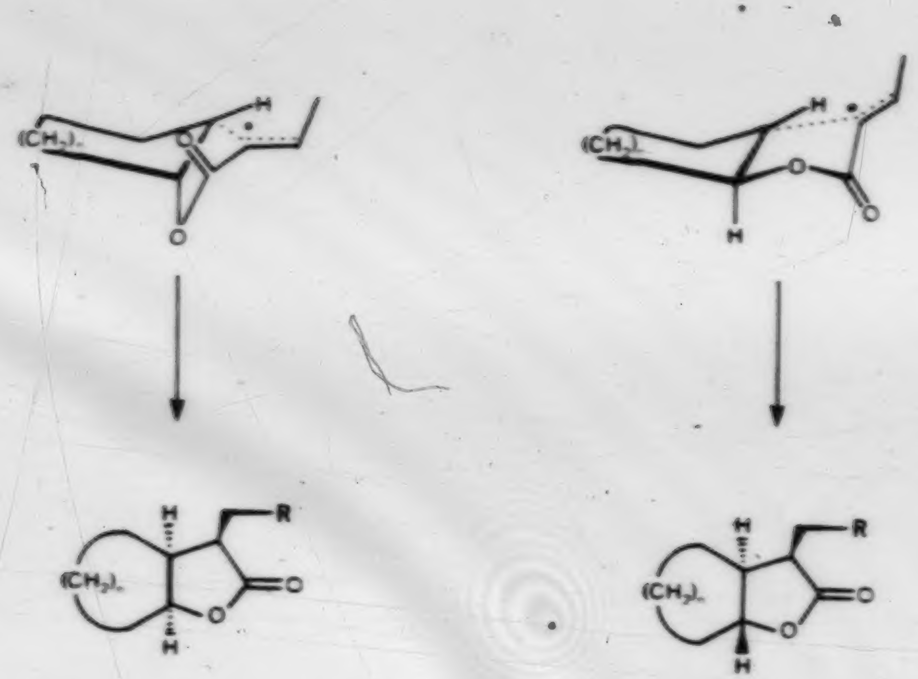


55

R = H, $CH_3$

n = 1, 2, 3

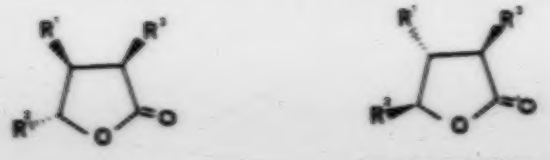
Figure 14


(CH2)n
H
O
O
(CH2)n
H
O
O
H
H
R
(CH2)n
O
O
H
H
R
(CH2)n
O
O
H

55

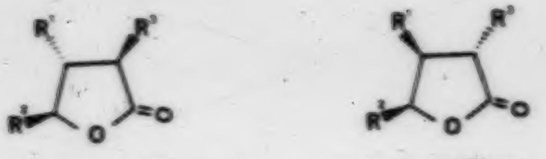
56

**Figure 15**



Predicted Major
**57**

Predicted Minor
**58**



Observed Major
**59**

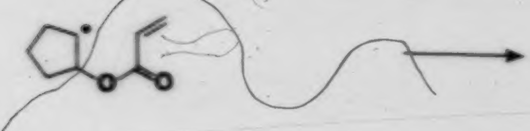
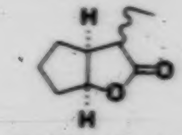
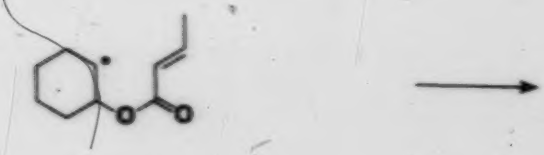
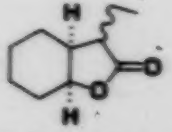
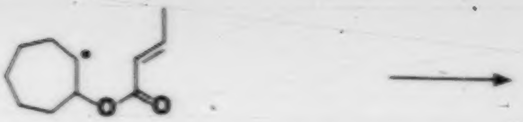
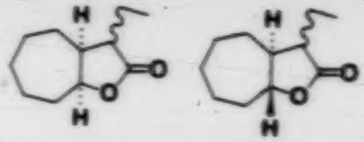
Observed Minor
**60**

reactions. It is evident that our system does not obey the Beckwith guidelines. The observed major isomer **59** (= **58**) is actually the one which is predicted to be formed in the least amount. One possible reason for the discrepancy is the constraint imposed on on the system by the ester unit which has to remain planar in the transition state. One must therefore exercise caution when applying the guidelines to systems containing heteroatoms and other functionality.

*iii) Nature of ring fusion geometry:* In cases where radical closure generates bicyclic systems, the ring fusion geometry requires comment. As shown in Table 13 (p. 106), [3.3.0] and [4.3.0] systems are generated with *cis*–ring fusion geometry whereas [5.3.0] systems exhibit both *cis*- and *trans*–ring fusion.

It is apparent that ring fusion geometry depends on the size of the ring that is initially present. When a 5–membered ring is being formed onto a preexisting 5– or 6–

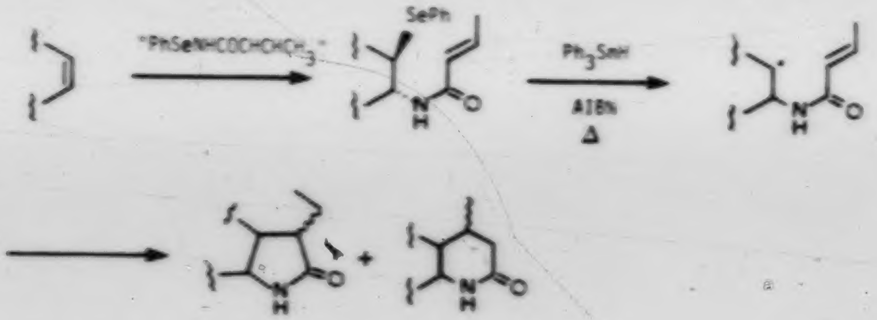
## TABLE 13
## RING FUSION GEOMETRY OF BICYCLIC LACTONES

| Radical | Bicyclic lactone(s) |
|---|---|
|  | <br>cis Ring Fusion |
|  | <br>cis Ring Fusion |
|  | <br>cis : trans<br>65 : 35 |

membered ring, the approach vector of the radical onto the olefinic unit of the pendant can be achieved much more easily via a transition state that leads to *cis*–ring fusion. When the initial ring is larger, as in the case of a 7–membered ring, this is no longer true and both transition states are energetically accessible. Similar phenomena are observed in the well known halolactonization reaction[108] (Table 14). The strain involved in the formation of a *trans*–ring fused [3.3.0] system[108] is probably responsible for the exclusive formation of *cis*–fused products in both radical cyclizations and halolactonizations, but the factors involved in the case of [4.3.0] and [5.3.0] systems remain uncertain.[109]

### C. Attempted Cyclization of β-(Phenylselenolamides

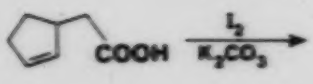
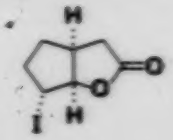
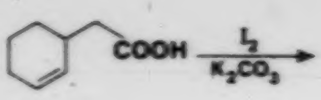
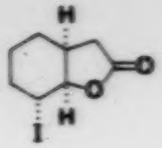
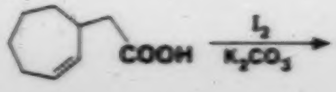
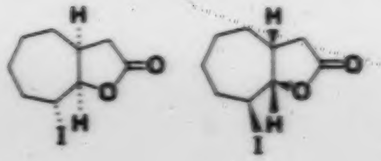
**a) Introduction**: It was of interest to find out if the radical cyclization reaction described above could be applied to the preparation of nitrogen heterocycles such as γ–lactams. Starting from alkenes, the methodology would require the attachment of "PhSe–NHCOCH=CHCH$_3$" across the double bond followed by radical induced cyclization (equ. 82).

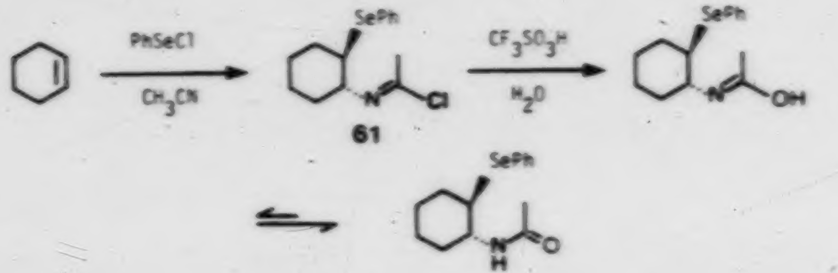


(equ. 82)

**b) Preparation of β–(phenylselenolamides:** Very few reactions are known that will allow the addition of "PhSe" and a nitrogen nucleophile across the double bond of an alkene.[110] One of these that was of interest to us was a new method for the addition of "PhSe" and "CH$_3$CONH" to olefins[111] (equ. 83).

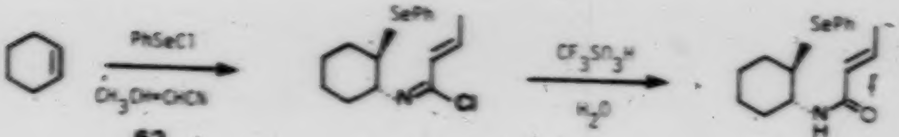
## TABLE 14
## HALOLACTONIZATION OF UNSATURATED CARBOXYLIC ACIDS

| Acids | Bicyclic lactone(s) |
|---|---|
|  COOH<br>$I_2$<br>$K_2CO_3$ |  |
|  COOH<br>$I_2$<br>$K_2CO_3$ |  |
|  COOH<br>$I_2$<br>$K_2CO_3$ |  |


PhSeCl
$CH_3CN$
SePh
N
Cl
61
$CF_3SO_3H$
$H_2O$
SePh
N
OH
SePh
N
H
O

(equ. 83)

in this reaction, acetonitrile behaves as a nucleophile. Intermediate iminochloride, 61, is then hydrolyzed to the amide. If 2–butenenitrile, 62 was to be used as the nucleophile, the end product, 63 should be of the type required for radical cyclization (equ.84).


PhSeCl
$CH_3CH=CHCN$
SePh
N
Cl
$CF_3SO_3H$
$H_2O$
SePh
N
H
O

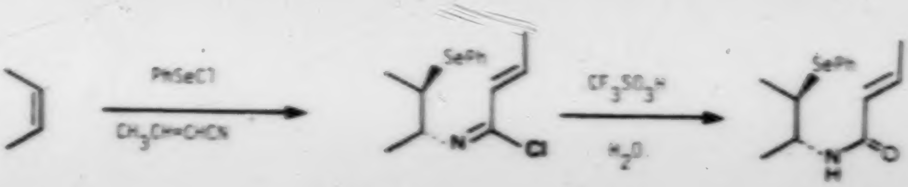
62

(55%)

63

(equ. 84)

In the event, when cyclohexene was treated with benzeneselenenyl chloride in the presence of a 2–Butenenitrile, 62 and the reaction mixture was hydrolyzed with aqueous trifluoromethanesulfonic acid, the desired $\beta$–(phenylselenol)amide was isolated in 55% yield. (Z)–2–Butene also gave the corresponding amide, 64 in 36% yield (equ. 85).*


PhSeCl
$CH_3CH=CHCN$
SePh
N
Cl
$CF_3SO_3H$
$H_2O$
SePh
N
H
O

(36%)

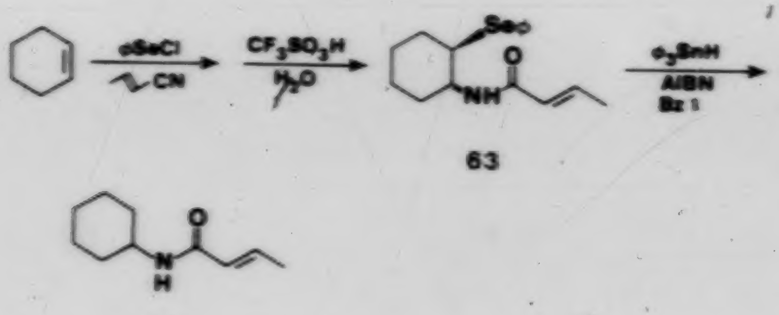
64

(equ. 85)

**c) Attempted cyclization of $\beta$–(phenylselenol)amides:** The next stage of the reaction involved generation of a radical by homolysis of the carbon–selenium bond. To this end, $\beta$–(phenylseleno)amide **63** was treated with a catalytic amount of AIBN and a small excess of triphenyltin hydride under conditions identical to those used for the formation of lactones from $\beta$–(phenylseleno)esters. However, the only product formed, **65**, was that derived from simple reduction without cyclization (equ. 86).

---

* The structure of amides 63 and 64 was determined on the basis of their spectral properties (IR, $^1H$ NMR, $^{13}C$ NMR); mass spectra and elemental analyses. The $^1H$ NMR was most diagnostic with resonances characteristic of the (E)–2–butenoic segment at $\delta$ 1.80(dd, J = 7, 2 Hz, 3H), 5.70(dq, J = 15, 2 Hz, 1H) and 6.80 (dq, J = 15, 7 Hz, 1H). The –CH–SePh protons were at $\delta$ 3.06 and 3.53 ppm for 63 and 64 and the –CH–NHCO protons at $\delta$ 3.86 and 4.35 ppm. In both cases, the NH proton could be seen at $\delta$ 5.67 ppm as a broad singlet. Both the exact mass spectra and the combustion analyses agreed with the predicted molecular formulas.

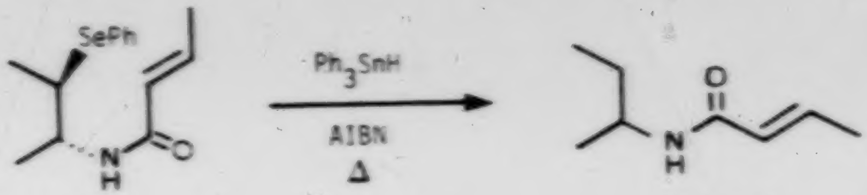


**63**

**65**

(equ. 86)

Similarly, **64** gave only the reduction product **66** (equ. 87).*



**64**

(75.7%)

**66**

(equ. 87)

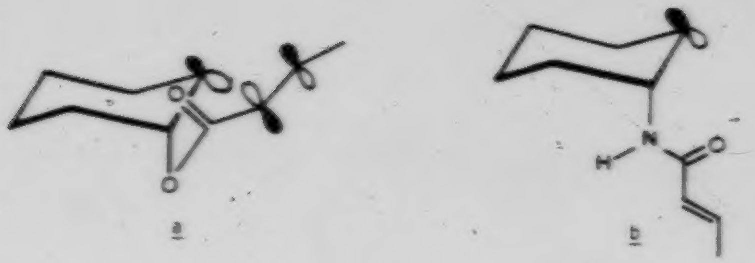
The failure of $\beta$–(phenylseleno)amides **65** and **66** to undergo radical cyclization may be due to a change in orientation of the pendant group. The ester linkage of $\beta$–(phenylseleno)esters must assume a conformation such that the carbon–carbon double bond is brought into proximity to the radical site and interaction between the half–filled *p*

---

*The identities of **65** and **66** were determined by $^1$H NMR analysis and confirmed by exact mass measurements, elemental analysis, IR and $^{13}$C NMR spectroscopy. Both **65** and **66** retained $^1$H NMR resonances characteristic of the (*E*)2–butenoic segment at $\delta$ 1.85 (dd, J = 7, 2 Hz, 3H), 5.80 (dq, J = 15, 2 Hz, 1H) and 6.85 (dq, J = 15, 7 Hz, 1H). The –CH–NHCO protons were still present at $\delta$ 3.86 and 3.98 ppm respectively for **65** and **66**, as was the NH proton at $\delta$ 5.4–5.5 ppm. The resonances characteristic of –CH–SePh had disappeared indicating removal of the phenylseleno group. In the case of cyclohexylamide **65**, the new symmetry of the molecule was revealed in the $^{13}$C NMR spectrum which showed only 8 resonances as opposed to ten in the original adduct **63**. The presence of an $\alpha,\beta$–unsaturated amide was confirmed by infrared absorptions at 3438 (NH), 3310 (NH), 1673 (C=O), 1633 (C=C) and 966 cm$^{-1}$ (C=C) in both **65** and **66**.

orbital and the antibonding π* orbital can occur (Fig. 16, a). The barrier between *cis* and *trans* conformation of esters is low (1–3 kcal/mol).[112]

Figure 16



a

b

As in the case of peptides,[112] the preferred conformation of amides is one in which the carbonyl oxygen is antiperiplanar to the hydrogen atom on the nitrogen. This brings the double bond out of reach of the *p* orbital at the radical site (Fig. 16, b) and the cyclization is no longer possible. Hydrogen transfer becomes the main process (Scheme 12) because the energy barrier (unlike the case with esters) between *cis* and *trans* conformations is high (18–25 kcal/mol).[112]

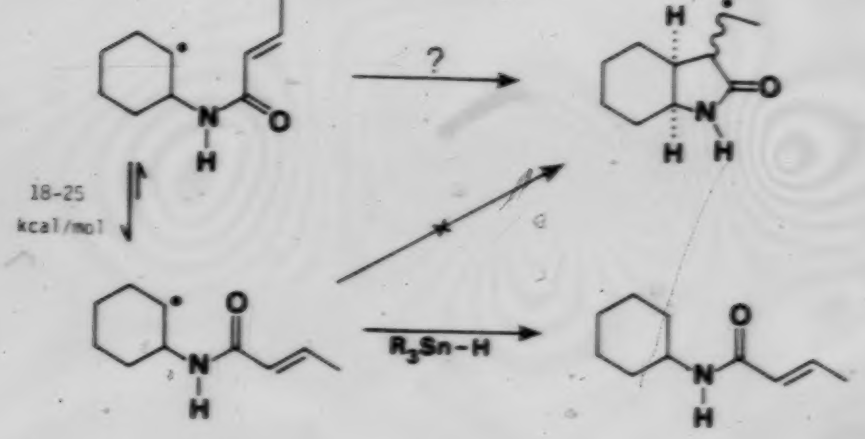
## D. Formation of Carbocycles by Radical Cyclization

### a) Introduction

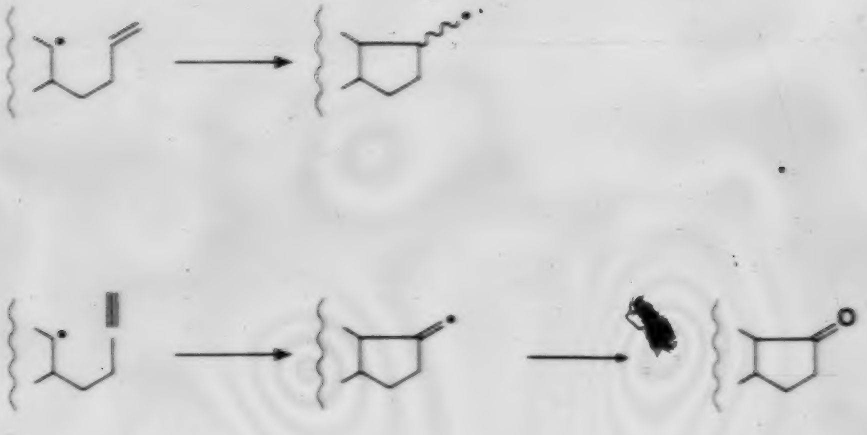
The first part of this work (p. 87–111) illustrates the concept of taking an olefin and, by means of an ionic process, attaching to it two units so chosen that a radical site could be generated from one of them while the other contained a suitably located multiple bond onto which the radical can cyclize. The idea was developed into a new method for preparation of γ-lactones. Our results suggested that this methodology would be very useful if applied to the formation of carbocycles (Scheme 13).

Of the two reactions shown, the second one, cyclization onto a digonal carbon, should be synthetically more useful because once the process has occurred, ozonolysis of the resulting double bond would serve to generate a carbonyl group, which can be

Scheme 12



Scheme 13

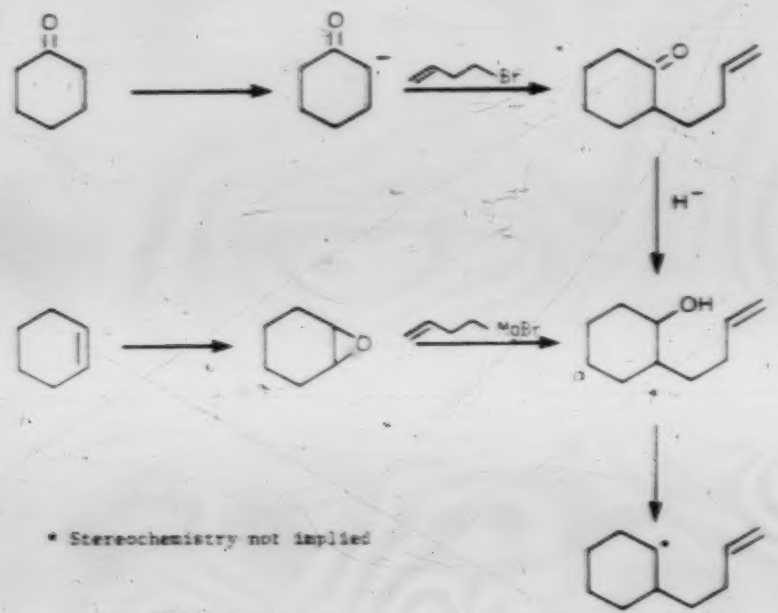


manipulated in a variety of ways. Even though there exists the possibility for both *exo*- and *endo*- modes of cyclization, only the former is expected to occur based on mechanistic work described in the introduction to this chapter. The reaction would therefore provide an entry to 5-membered rings (starting from 5-hexenyl radicals). If 6-

heptynyl radicals are generated, then 6-membered rings would be expected. Such reactions are of obvious synthetic utility. The use of easily accessible substrates for cyclization was, of course, important in order to make the process versatile.

As in the cyclization of β-(phenylselenolesters, the first step was to attach two units to an appropriate starting material. One unit would serve to generate a radical and the other would be a carbon chain containing a properly positioned π-system. We expected that alkylation technology would provide an efficient and versatile method for introduction of the unsaturated carbon chain. Ketones and epoxides could then serve as starting materials (Scheme 14) depending on whether the alkylating agent was an electrophile or a nucleophile.

**Scheme 14**



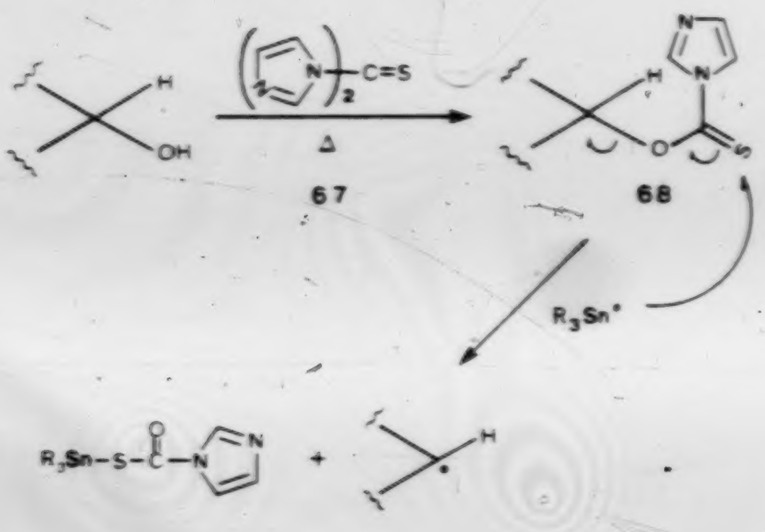
* Stereochemistry not implied

As shown in Scheme 14, the hydroxyl group has to serve as a precursor to the radical and this choice was made because several methods are available for generating carbon radicals from alcohols. Conversion to a halide and homolysis of the carbon–

halogen bond with tin radicals is an obvious procedure and has, in fact, been used in most mechanistic studies (see Introduction). However, alkyl halides are often unstable and are sometimes difficult to prepare.

Recently, Barton[111] developed a procedure for homolytic cleavage of carbon–oxygen bonds in secondary alcohols (Scheme 15) and this method appeared ideal for our purposes. It involves esterification of an alcohol with 1,1'-thiocarbonylbisimidazole **67** under mild and neutral conditions. The resulting alkoxythiocarbonylimidazoles **68** are stable and easily purified by chromatography. Treatment with tin radicals results in clean homolysis of the carbon–oxygen bond.

**Scheme 15**



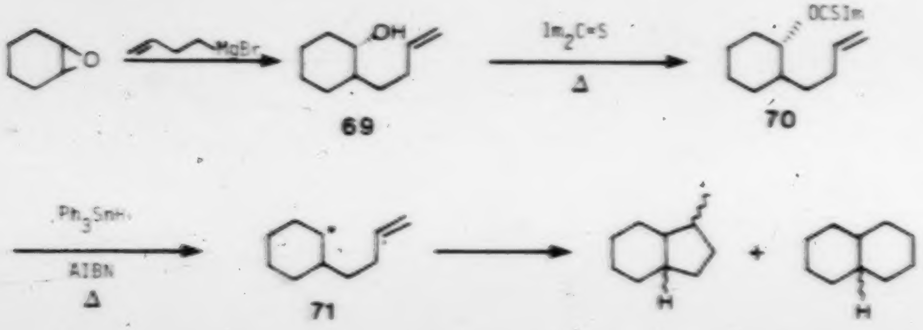
This reaction is applicable only to secondary alcohols. Tertiary alcohols do not react with 1,1'-thiocarbonylbisimidazole **67** and the sulfur derivatives of primary alcohols, though easily formed, undergo cleavage to alkoxy, instead of carbon radicals. Alkoxythiocarbonylimidazoles such as **68**, are not the only sulfur derivatives useful in alcohol deoxygenations[114] but they proved eminently suitable for our purposes

### b) Carbocycles by Cyclization onto C=C:

### i) Results and Discussion

The use of epoxides as starting materials was investigated first. As shown in Scheme 16, treatment of cyclohexene oxide with the appropriate unsaturated Grignard reagent should give alcohol **69**. Esterification with **67** would then afford alkoxythiocarbonylimidazole **70** which is properly constituted to undergo the radical cyclization.

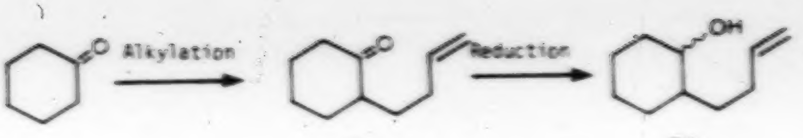
**Scheme 16**



Im = N-Imidazoyl

We tested the suitability of alkoxythiocarbonylimidazoles for the ring closure with compound **70** and we made this choice because it is known that radical **71**, made in a different way, undergoes closure in good yield[115]. In the event, when cyclohexene oxide was treated with the Grignard reagent formed from 4-bromo-1-butene in ether, the desired alcohol, **69**, could not be isolated. Various temperatures in the range −60 to +25°C and other solvents, such as dioxane and THF, were examined but without success. Consequently, epoxides were rejected as potential starting materials. Admittedly, an exhaustive investigation was not made, but our aim at this stage was to examine the chemistry of thiocarbonylimidazolides.

Alkylation technology would be expected to provide ready access to δ-alkenols such as **73** (equ. 88).



72 73

(equ. 88)

and we prepared 2-(3-butenyl)-cyclohexanone **72** by alkylation of *N*-cyclohexylidene-cyclohexanamine **74** (Scheme 17). Reduction of the ketone with lithium aluminum hydride gave alcohols **73a** and **73b** in 72% yield overall from the imine **74**.

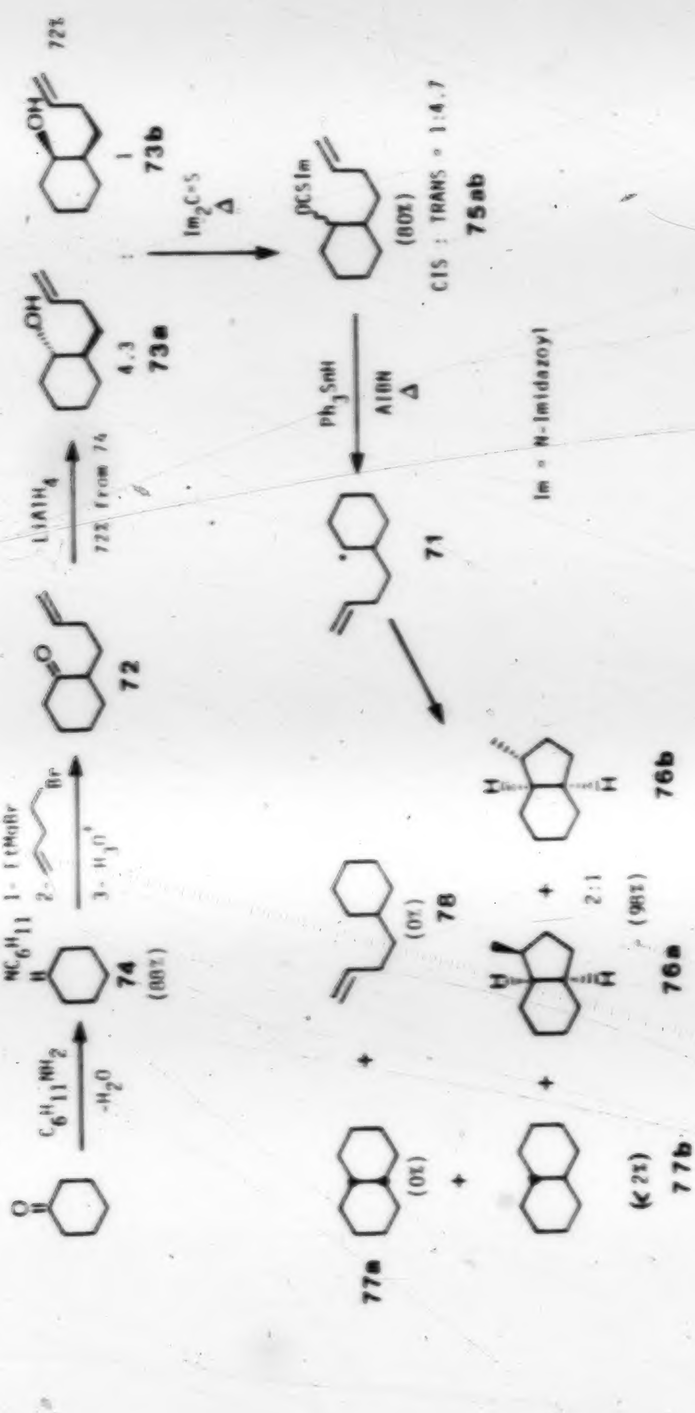
The mixture of *cis* and *trans* alcohols **73ab** was esterified with 1,1'-thiocarbonyl-bisimidazole **67** to give alkoxythiocarbonylimidazoles **75ab**, and radical **71** was generated cleanly upon treatment with triphenyltin radicals. It underwent regioselective closure to octahydroindenes **76ab** (67.7% yield). A small amount (1.4%) of *trans*-decahydro-naphthalene **77b** was also formed. *cis*-Decahydronaphthalene **77a** and the product **78** of hydrogen transfer to radical **71** were not detected ($^1$H NMR, $^{13}$C NMR, VPC). The absence of **78** is a consequence of the experimental procedure that we have followed. This involves slow addition of the reagents over *ca.* 15 h and the use of dilute solutions. As in the tin hydride reduction of 2-(3-butenyl)-1-chloro-cyclohexane[111] radical **71** underwent almost exclusive (98%) 5-*exo*-closure. 6-*Endo*-products were present only in trace amounts (<2%). These results have been rationalized in terms of stereoelectronic control (see Introduction, p. 66). As expected, the products derived from 5-*exo*-closure, **76ab**, had *cis*-ring fusion geometry. The corresponding *trans*-ring fused octahydroindenes were present only in trace amounts (<1%). Similar behavior was observed in the lactonization experiments when a 5-membered ring was being formed on a pre-existing 6-membered ring.

The octahydroindenes **76** were produced as a mixture of *exo*- and *endo*- isomers in a ratio of 1:2.* This observation is consistent with Beckwith's results which were

---

* The assignment was by analogy to the ring closure of **71** derived from 2-(3-butenyl)-1-chlorocyclohexane.[117] *trans*-Decahydronaphthalene **77b** was identified by comparison with an authentic sample.

Scheme 17

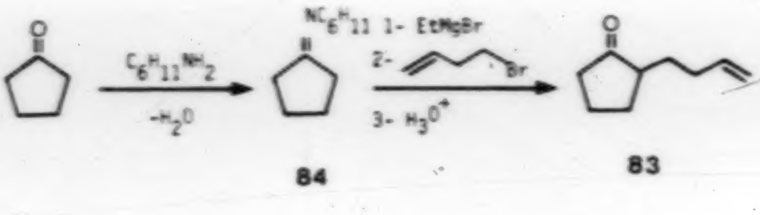

C6H11NH2
-H2O
NC6H11
74
(88%)
1- EtMgBr
2-
Br
3- H3O+
72
LiAlH4
72% from 74
OH
4.3
73a
OH
1
73b
72%
Im2C=S
Δ
OCSIm
(80%)
CIS : TRANS = 1:4.7
75ab
Ph3SnH
AIBN
Δ
71
Im = N-Imidazoyl
77a
(0%)
78
(0%)
H
H
76a
76b
2:1
(98%)
(< 2%)
77b

discussed earlier (p. 66).

Having established the use of secondary hydroxyl groups as a source of radicals in ring closure reactions, it was necessary to test the concept with several other substrates in order to demonstrate its generality as a synthetic method.

When applied to acyclic substrates, the reaction leads to the formation of substituted cyclopentanes (Scheme 18). Alcohol **79** was formed in about 54% yield from *n*-octanal. After esterification to alkoxythiocarbonylimidazole **80** (73%), radical **81** was generated in the usual manner and cyclization occurred to give a 63.5% yield of *cis*- and *trans*-1-heptyl-2-methyl-cyclopentanes **82**. Ring closure again took place exclusively via the 5-*exo*- mode. Compound **82** was obtained as a mixture of isomers in a ratio of 1:2.5. The relative stereochemistry could not be assigned on spectroscopic grounds. However, radical **81** is a C-1 substituted 5-hexenyl radical and, according to Beckwith's guidelines, the major isomer is expected to have *cis*-stereochemistry.

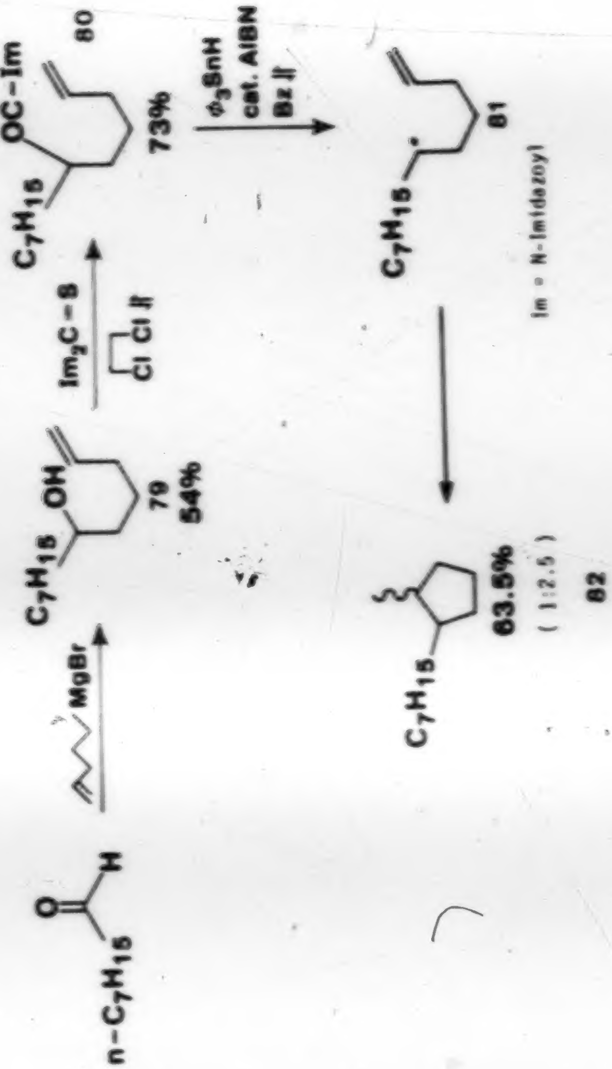
To investigate the formation of [3.3.0] systems we attempted to prepare 2-(3-butenyl)cyclopentanone **83** by alkylation of cyclopentanone. When imine **84** was deprotonated (equ. 89) and treated with 4-bromo-1-butene under conditions that were successful in the case of the 6-membered derivative, no alkylation products were isolated.



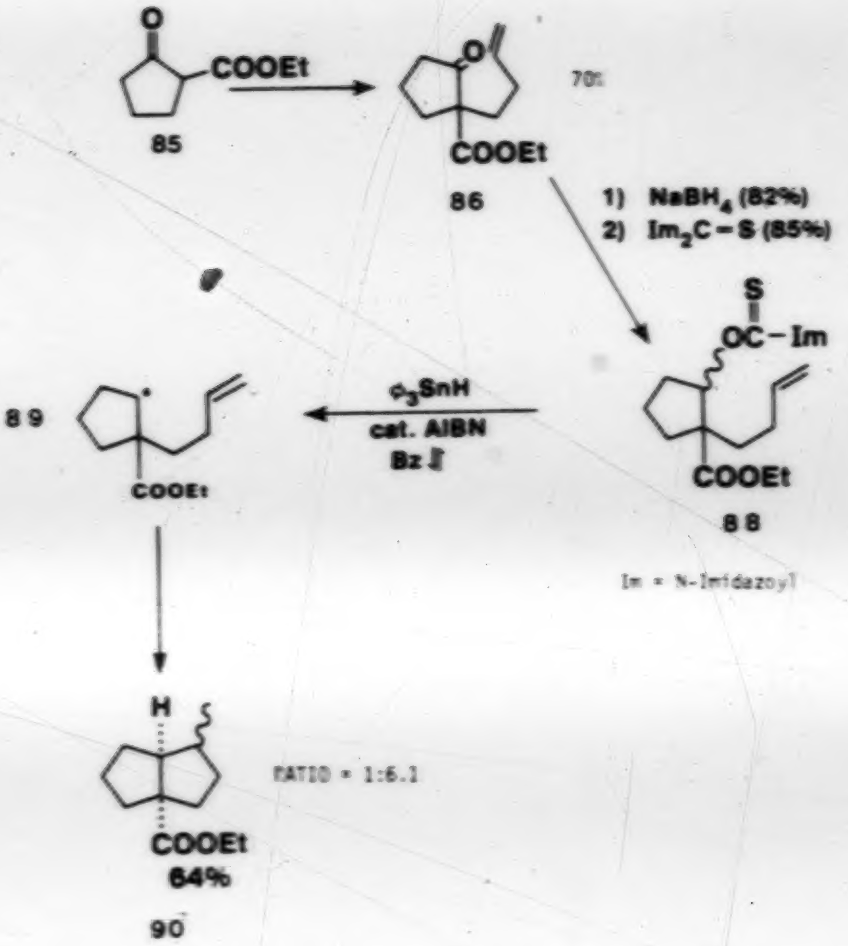
(equ. 89)

Alkylation of ketoester **85** on the other hand was easily carried out (Scheme 19) following a procedure described in the literature.[114] The ketoester **86** was then reduced to

Scheme 18


n-C7H15
O
H
MgBr
C7H15
OH
79
54%
Im2C=S
Cl Cl //
C7H15
S
OC-Im
73%
80
φ3SnH
cat. AIBN
Bz //
C7H15
81
C7H15
63.5%
( 1:2.5 )
82
Im = N-Imidazoyl

Scheme 19


O
COOEt
85
O
COOEt
86
70%
1) NaBH$_4$ (82%)
2) Im$_2$C=S (85%)
S
OC−Im
COOEt
88
Im = N-Imidazoyl
$\phi_3$SnH
cat. AIBN
BzH
89
COOEt
H
COOEt
64%
90
RATIO = 1:6.1

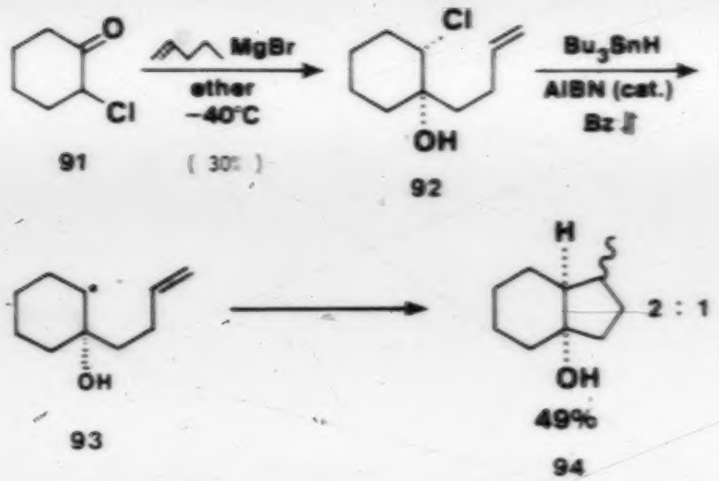
the corresponding alcohol **87** (as a mixture of isomers), and esterified to alkoxythiocarbonylimidazoles **88** (also as a mixture of isomers). Treatment with triphenyltin hydride in the presence of AIBN gave radical **89**. The radical underwent ring closure to the pentalene derivative **90** in 64% yield (Scheme 19). The product was formed as a 1.6:1 mixture of isomers, reflecting a certain degreeof stereoselectivity. The only type of cyclization detectable by $^1$H NMR (400 MHz) was the 5-*exo*-mode. The *cis*-ring fusion geometry of compound **90** was assigned on the basis of the strain involved in making *trans*-fused [3.3.0] systems.[109] This experiment also demonstrates that the tin radical induced cyclization is compatible with the ester functionality.

In the next example, we demonstrated that hydroxyl groups also do not interfere in the ring closure (Scheme 20). Condensation of 2-chloro-cyclohexanone **91** with 3-butenylmagnesium bromide gave the chlorohydrin **92** in 30% yield. Homolysis of the carbon—chlorine bond with tri-n-butyltin radicals in the usual way gave **93** which underwent regiospecific closure to the octahydroindenol **94** in 49% yield. The product was formed as a 2:1 mixture of compounds isomeric at C-1. The moderate yield was due to difficulties in separating the cyclized material from tin-containing side products (such as hexabutylditin and tri-n-butyltin chloride). The two isomers could not be differentiated on the basis of their spectroscopic properties but, by analogy with the 2-(3-butenyl)-cyclohexyl radical, one expects the major isomer to have the C-1 methyl group in the *endo*-orientation (i.e. *trans* to the hydroxyl group).

### ii) Conclusion

In the cases studied, cyclization was found to occur exclusively in the *exo*-mode. This is a consequence of the structure of the transition state for alkyl radical additions to double bonds (Fig. 5, p. 60). In each example, the required alignment of atoms is more readily accommodated by a transition state leading to *exo*- products. All bicyclic products that were formed by closure of a 5-membered ring onto a pre-existing 5- or 6-membered ring had *cis*-ring fusion geometry. In the case of octahydroindene derivatives with a methyl substituent at C-1, the stereochemistry at that position could not be determined on spectroscopic grounds. However, by analogy to the 2-(3-butenyl)-cyclohexyl radical, it can be assumed that the major isomer is the one bearing the C-1

Scheme 20



substituent in the *endo*– conformation (i.e. *trans* to the adjacent bridgehead hydrogen). The degree of stereoselectivity at the 1–position varied with the structure of the 5–hexenyl radical.

It is clear that cyclization of radicals onto double bonds is a process that may be synthetically useful. In each reaction, a carbon–carbon bond is formed regiospecifically.

One feature inherent in this type of reaction, and one that presents a disadvantage, is the fact that functionality is destroyed as a result of cyclization. The double bond originally present in the substrate is converted into a methyl group. Consequently, further elaboration is difficult and one must then rely on functionality already present in other parts of the molecule. In this connection, we have demonstrated that the reaction can be carried out in the presence of various groups such as ester and hydroxyl.

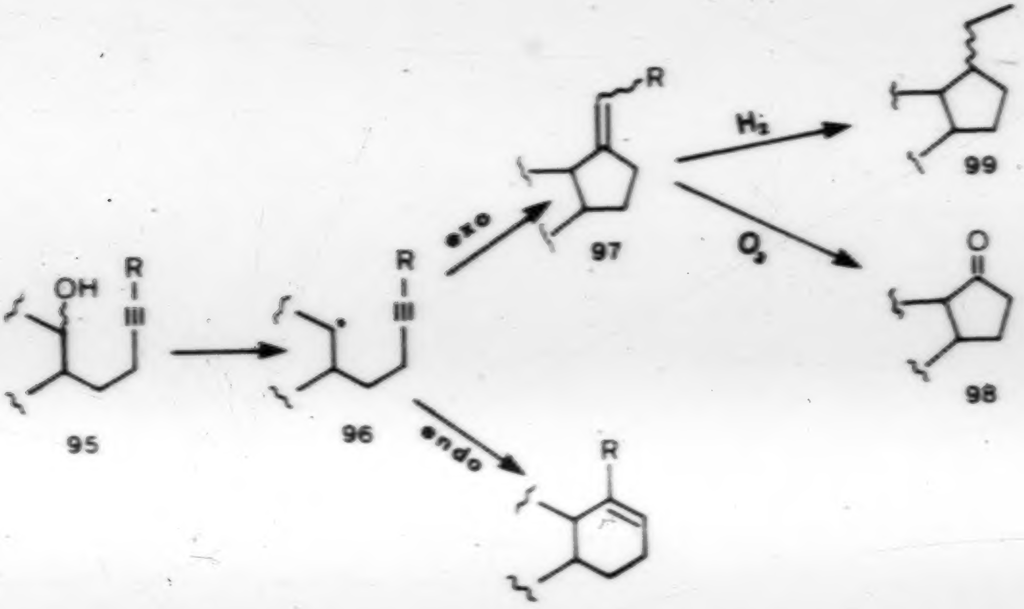
A cyclization process that would introduce new functionality or simply modify functionality already present would be much more useful synthetically. The remaining parts of this thesis are devoted to the development of such a process

### c) Carbocycles by Cyclization onto C≡C:

#### i) Introduction:

As mentioned earlier, ring closure of a radical onto a carbon–carbon triple bond can lead to the formation of cyclic compounds that have a double bond *exo*– or *endo*–cyclic to the newly formed ring, depending on the mode of closure (Scheme 2.1).

**Scheme 21**

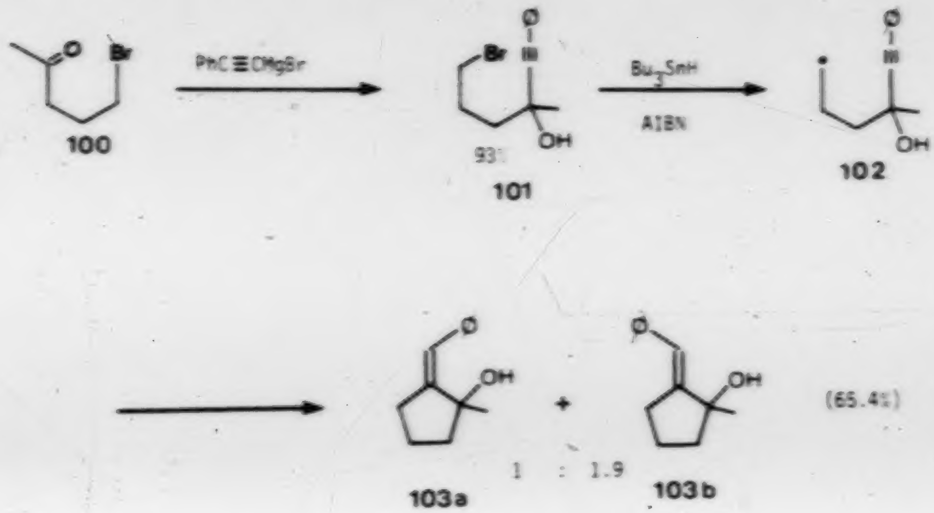


This double bond can, of course, be further manipulated in a variety of ways. For example, ozonolysis of **97** would provide a route to cyclopentanone **98** and hydrogenation should give products **99** of the type obtained by radical cyclization of olefins, but perhaps, with increased stereoselectivity.

**ii) Results and discussion:**

Our initial efforts were focussed on the generation of readily available acyclic 5-hexynyl radicals, in order to investigate the cyclization process itself. Scheme 22 summarizes the preparation of a substrate of this type and its cyclization.

**Scheme 22**



Bromoalcohol **101** was easily produced in high yield as shown.* Homolysis of the carbon–bromine bond with tri-*n*-butyltin radicals gave intermediate **102** which cyclized to the benzylidene cyclopentanones **103a** and **103b** (65%) in a ratio of 1:1.9.** This experiment demonstrates that, like 5-hexenyl radicals, 5-hexynyl radicals undergo exclusive closure via the *exo*- pathway to produce cyclopentane derivatives in a synthetically useful yield.

---

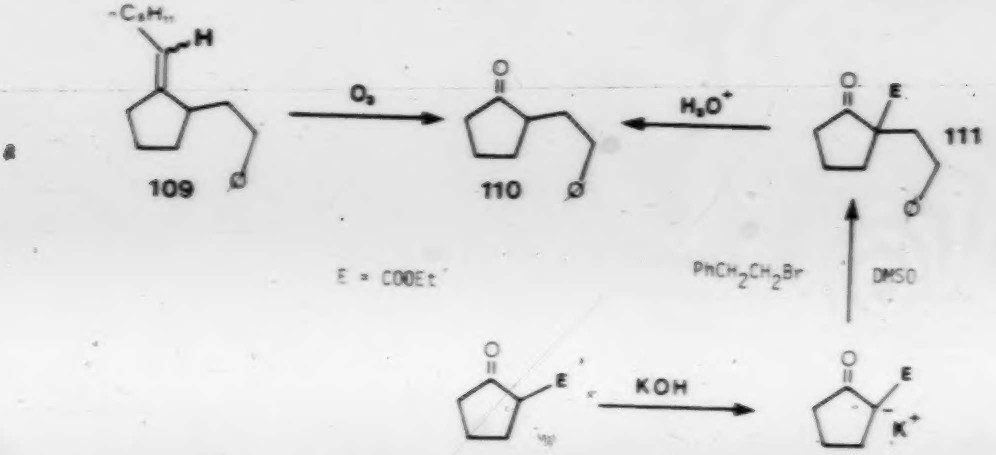
* The lithium salt corresponding to the bromomagnesium salt of phenylacetylene did not give the desired alcohol.

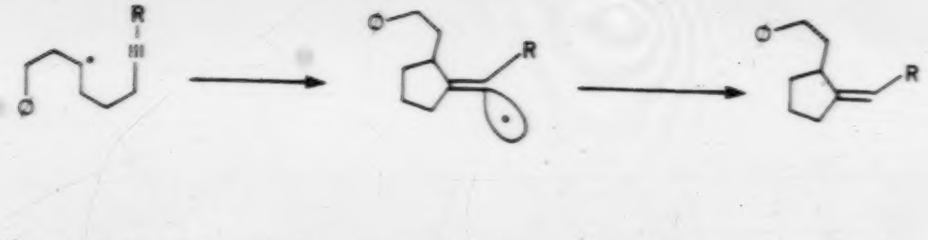
**The geometry of the substituted double bond was assigned tentatively on the basis of chemical shifts in the $^1$H NMR (400 MHz) spectrum of the separated isomers. **103a** shows deshielding of two aromatic protons due to their proximity to the hydroxyl group. For the same reason, the olefinic hydrogen of **103b** occurs at a lower field than in **103a** (see Experimental section).

Another acyclic case was investigated (Scheme 23) with equally encouraging results. Alkylation of the lithium salt of 1-heptyne **104** with the tetrahydropyranyl ether of 4-bromo-1-butanol in THF–HMPA gave alcohol **105** (30%) as shown. Oxidation with pyridinium chlorochromate gave the corresponding aldehyde, which was condensed with phenethylmagnesium chloride without purification. Alcohol **106** (66%) was then esterified with 1,1'-thiocarbonyldiimidazole **67** (65%) and radical **108** was subsequently generated in the usual manner. This radical also underwent regiospecific 5-*exo*-closure to a single compound **109** in 81%.*

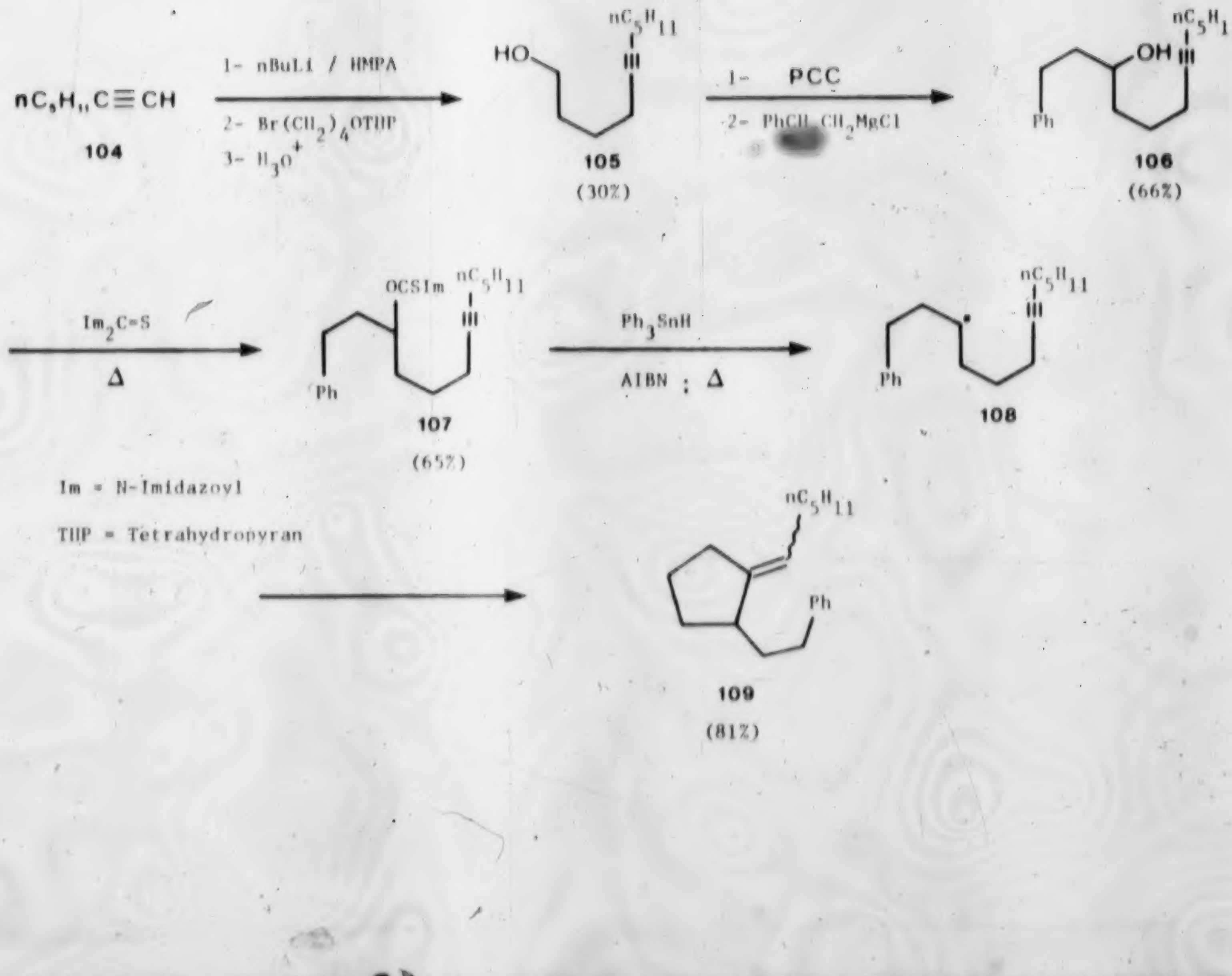
---

*The alkylation of **104** was not optimized. The structure of compound **109** was determined unequivocally by ozonolysis to cyclopentanone **110**. This ketone was identical with an authentic sample[14] prepared as shown below.





The geometry of the substituent on the double bond could not be determined on the basis of the spectral data available. However, radicals are known to add to carbon–carbon triple bonds in an *anti*- fashion (see Introduction) and therefore, one would expect preferential formation of the (*Z*)-isomer.


nC₅H₁₁C≡CH
104
1- nBuLi / HMPA
2- Br(CH2)4OTHP
3- H3O+
HO
nC5H11
105
(30%)
1- PCC
2- PhCH2CH2MgCl
OH
nC5H11
Ph
106
(66%)
Im2C=S
Δ
OCSIm
nC5H11
Ph
107
(65%)
Ph3SnH
AIBN ; Δ
nC5H11
Ph
108
nC5H11
Ph
109
(81%)

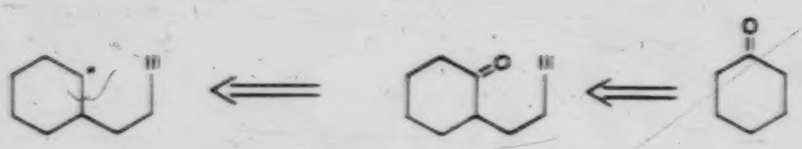
Scheme 23

Im = N-Imidazoyl

THP = Tetrahydropyran

Having shown that 5-hexynyl radicals generated from alkoxythiocarbonylimidazoles undergo ring closure in the manner indicated, we wanted to further develop this process into a new synthetic method that would allow elaboration of a simple starting material into carbocyclic compounds. As mentioned in the introduction there are very few cases in the literature where cyclization of a radical onto a C≡C bond is used in synthesis for the formation of a carbocycle. To our knowledge, this type of process has not been investigated to any great extent and the development of such methodology should prove very useful in preparative chemistry.

Our efforts were first concentrated on the formation of 2-(3-butynyl) radicals such as **112**.

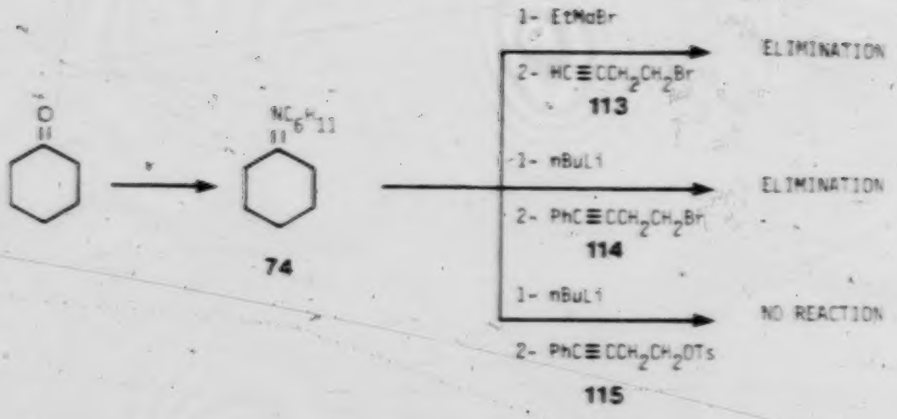


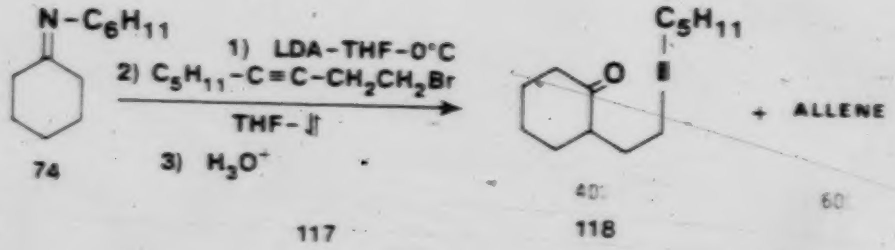
**112**

(equ 90)

This species should be available, *a priori*, through alkylation technology (equ 90) as were the alkene counterparts. Unfortunately, all attempts at alkylating cyclohexanone with homopropargylic derivatives were unsuccessful (Scheme 24). When bromides **113** and **114** were subjected to the basic environment of the anion of imine **74**, they underwent dehydrohalogenation to conjugated enynes. Tosylate **115** on the other hand was totally unreactive and was recovered unchanged after exposure for 20 h to the lithium salt of the imine at 60°C. When imine anion **116** (generated by treatment of imine **74** with LDA) was treated with 1-bromo-3-nonyne **117**, alkylation occurred but the product consisted of a mixture of the desired 2-(3-nonynyl)-cyclohexanone **118** (40%) and a substance containing an allene group (60%). The two could not be separated by chromatography or by distillation (equ 91).

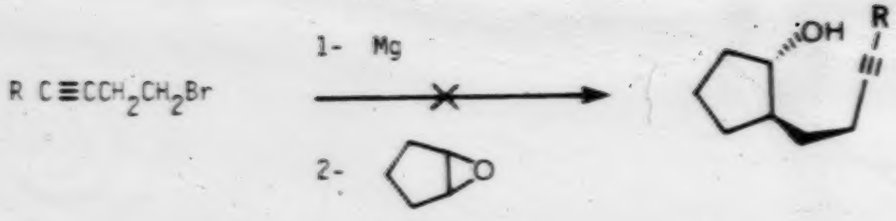
**Scheme 24**


O
NC6H11
74
1- EtMgBr
2- HC≡CCH2CH2Br
113
ELIMINATION
1- nBuLi
2- PhC≡CCH2CH2Br
114
ELIMINATION
1- nBuLi
2- PhC≡CCH2CH2OTs
115
NO REACTION


N-C6H11
74
1) LDA-THF-0°C
2) C5H11-C≡C-CH2CH2Br
THF-⥮
3) H3O+
117
C5H11
O
118
+ ALLENE
40
60

(equ 91)

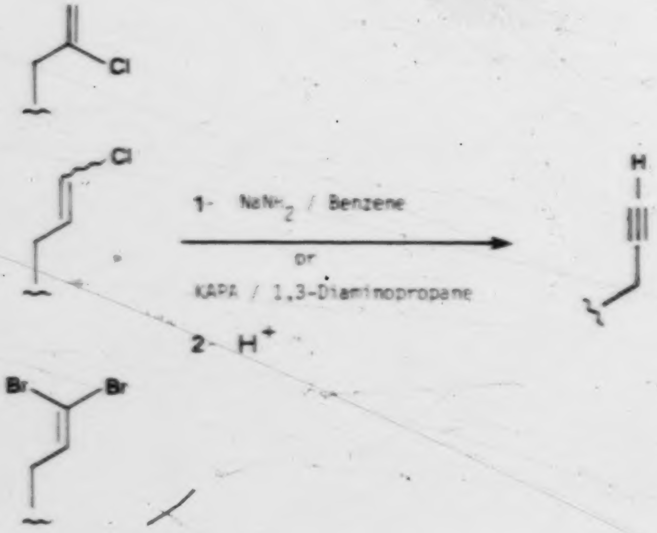
Attempts at opening epoxides with Grignard reagents derived from homopropargylic bromides (equ 92) were equally unsuccessful.


R C≡CCH2CH2Br
1- Mg
2-
OH
R

(equ 92)

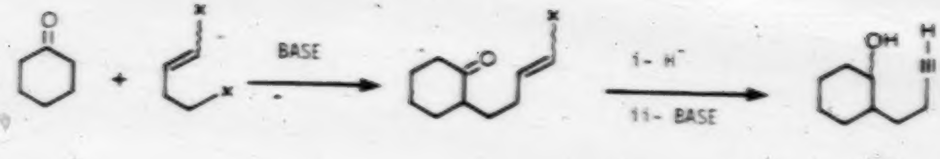
$R = nC_5H_{11}$, Ph

Since we were not able to use homopropargylic compounds for the preparation of δ-acetylenic alcohols or ketones we examined the use of masked acetylenes in the form of vinyl halides. These have been used widely in synthesis[112] and when treated with a strong base, such as sodium amide in refluxing benzene, or the potassium salt of 1,3-diaminopropane[113] (KAPA), they undergo elimination to acetylenic species (equ 93)


Cl
Cl
Br
Br
1- NaNH2 / Benzene
or
KAPA / 1,3-Diaminopropane
2- H+
H

(equ 93)

To apply this approach to the present problem would require alkylation of a cyclohexanone with a homoallylic vinyl halide followed by base-induced elimination (equ 94).



119 (equ 94)

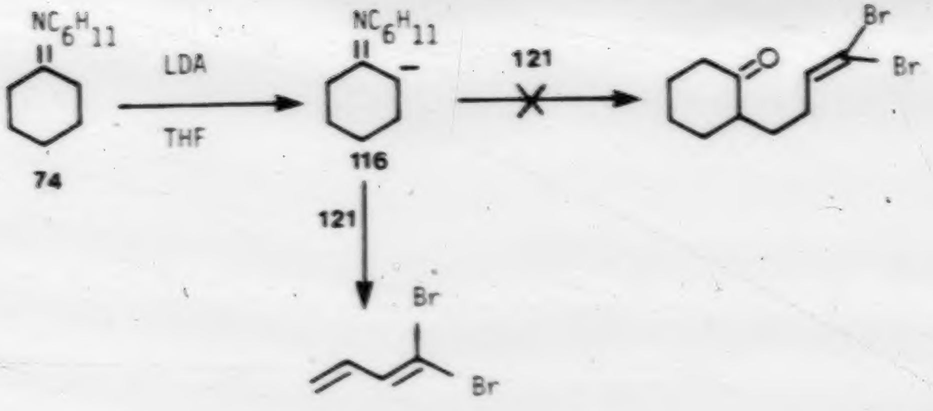
Corey recently developed a method for homologation of aldehydes to acetylenes via a Wittig-type reaction[119] (equ 95) and this procedure should allow preparation of 1,1,4-tribromo-1-butene **121** when applied to 3-bromo-propanal **120** (equ 96)

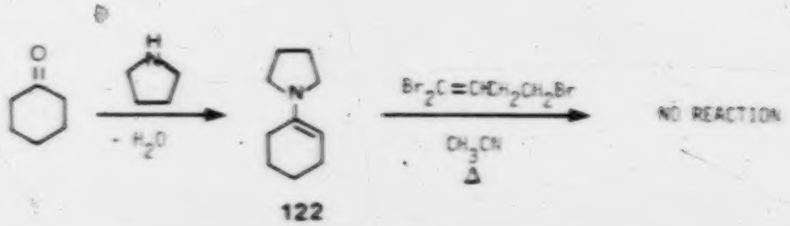
$$\mathrm{RCHO} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{Ph_3P{=}CBr_2}} \mathrm{RCH{=}CBr_2} \xrightarrow{\mathrm{nBuLi}} \mathrm{RC{\equiv}CH} \qquad \text{(equ 95)}$$

$$\mathrm{CH_2{=}CHCHO} \xrightarrow{\mathrm{HBr}} \underset{\mathbf{120}}{\mathrm{BrCH_2CH_2CHO}} \xrightarrow{\mathrm{Ph_3P{=}CBr_2}} \underset{\mathbf{121}}{\mathrm{BrCH_2CH_2CH{=}CBr_2}} \qquad \text{(equ 96)}$$

Tribromide **121** was successfully prepared in this way. However, when treated with imine anion **116**, the alkylating agent suffered loss of HBr and alkylation products were not formed (Scheme 25). When bromide **121** was refluxed in acetonitrile with the pyrrolidine enamine of cyclohexanone **122** no reaction occurred and the bromide was recovered (equ 97).

**Scheme 25**


NC$_6$H$_{11}$
LDA
THF
74
NC$_6$H$_{11}$
116
121
Br
Br
121
Br
Br

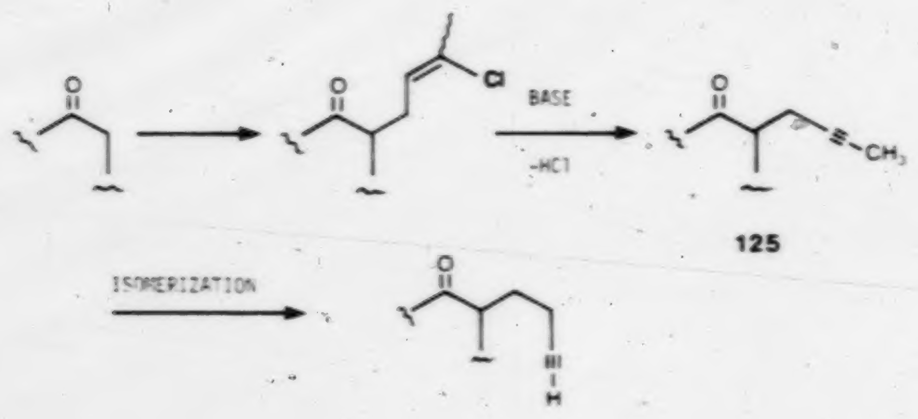

O
H
N
- H$_2$O
N
122
Br$_2$C=CHCH$_2$CH$_2$Br
CH$_3$CN
Δ
NO REACTION

(equ 97)

The use of (*E*)- and (*Z*)-3-chloro-1-iodo-2-butene **123** and (*E*)- and (*Z*)-1,3-dichloro-2-butene **124** were investigated next as possible 3-butynyl synthons (Scheme

27, p. 133). They were expected to be more resistant towards base-induced dehydrohalogenations (as they are not homoallylic species) and both **123** and **124** are more reactive than bromide **121**. It was expected that alkylation with these vinyl halides, and dehydrohalogenation would give methylacetylenes **125** that would then require isomerization (Scheme 26).

**Scheme 26**

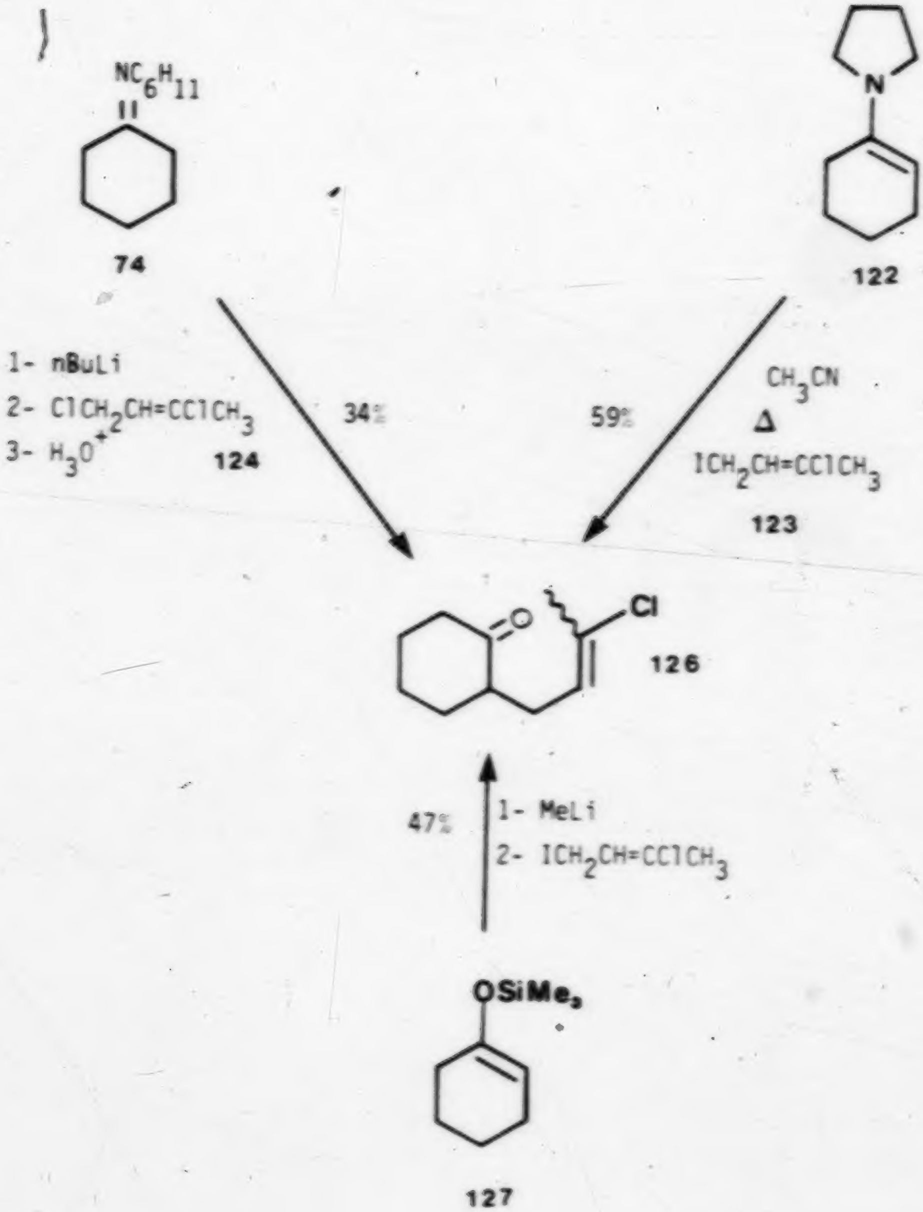


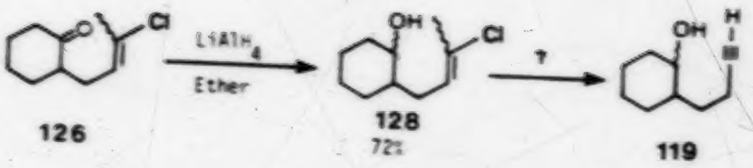
**125**

Both alkylating agents were found to be adequate for the preparation of (*E*)- and (*Z*)-2-(3-chloro-2-butenyl)-cyclohexanone **126** (Scheme 27) and anions derived from imine **74** or trimethylsilyl enol ether **127** gave the desired chloroketone **126**. However, the best yields were obtained in the enamine reaction between iodide **123** and pyrrolidine enamine **122** (Scheme 27).

The carbonyl group in ketone **126** was reduced with lithium aluminum hydride to give a mixture of four isomeric alcohols **128** (equ. 98).

**Scheme 27**

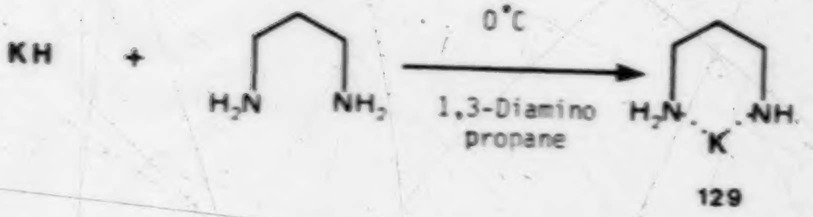

NC$_6$H$_{11}$
74
122
1- nBuLi
2- ClCH$_2$CH=CClCH$_3$
3- H$_3$O$^+$
124
34%
59%
CH$_3$CN
Δ
ICH$_2$CH=CClCH$_3$
123
N
O
Cl
126
47%
1- MeLi
2- ICH$_2$CH=CClCH$_3$
OSiMe$_3$
127



(equ 98)

The transformation of 128 into δ-acetylenic alcohol 119 requires dehalogenation of the vinylchloride to the corresponding methyl acetylene followed by isomerization of the triple bond to the terminal position. The base of choice for this type of isomerization is the potassium salt of 1,3-diaminopropane[111] (KAPA) 129 (Scheme 28).

**Scheme 28**

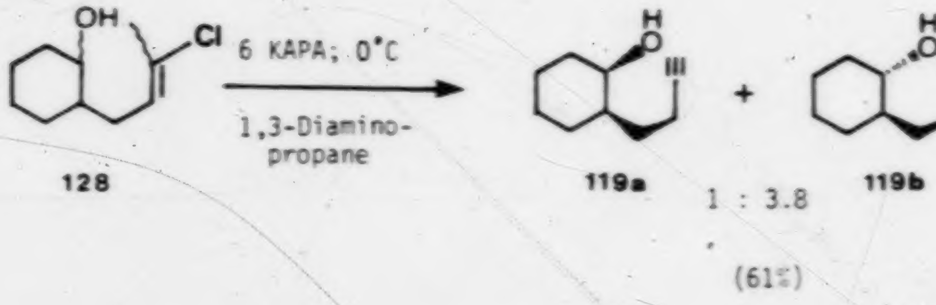


$$R-C\equiv C-(CH_2)_n-CH_3 \xrightarrow[< 0\,°C]{KAPA} R-(CH_2)_{n+1}-C\equiv C^-\ K^+$$

$$\xrightarrow{H_3O^+} R-(CH_2)_{n+1}-C\equiv CH$$

Since vinyl halides are more acidic than hydrocarbons, KAPA is expected to cause both dehalogenation and isomerization of the resulting triple bond. When alcohol 128 was subjected to the action of a large excess of the base (6 equ.) in 1,3-diaminopropane at

0°C. 2-(3-butynyl)cyclohexanol **119** was obtained as a mixture of *cis*- and *trans*-isomers (61%) in a ratio of 1:3.8 (equ. 99).



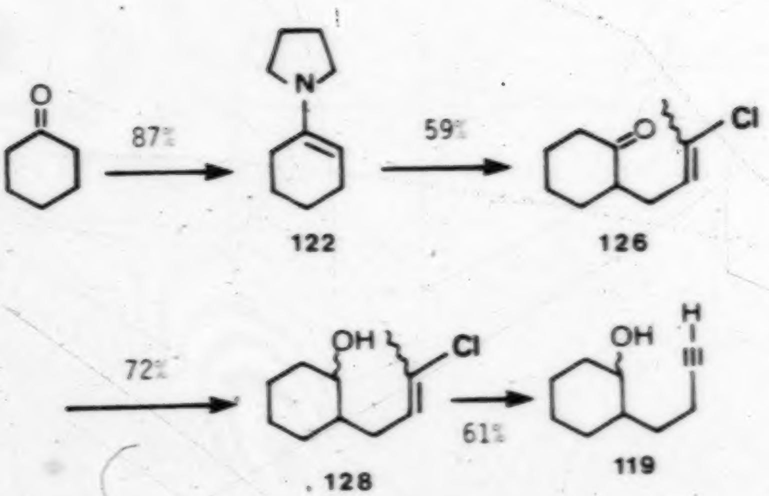
(equ. 99)

The conversion of cyclohexanone to alcohols **119** is summarized in Scheme 29, the overall yield for the four steps being 22.6%. Even though this approach was relatively viable, we investigated an alternative route to **119** via successive alkylation and isomerization reactions (Scheme 30).

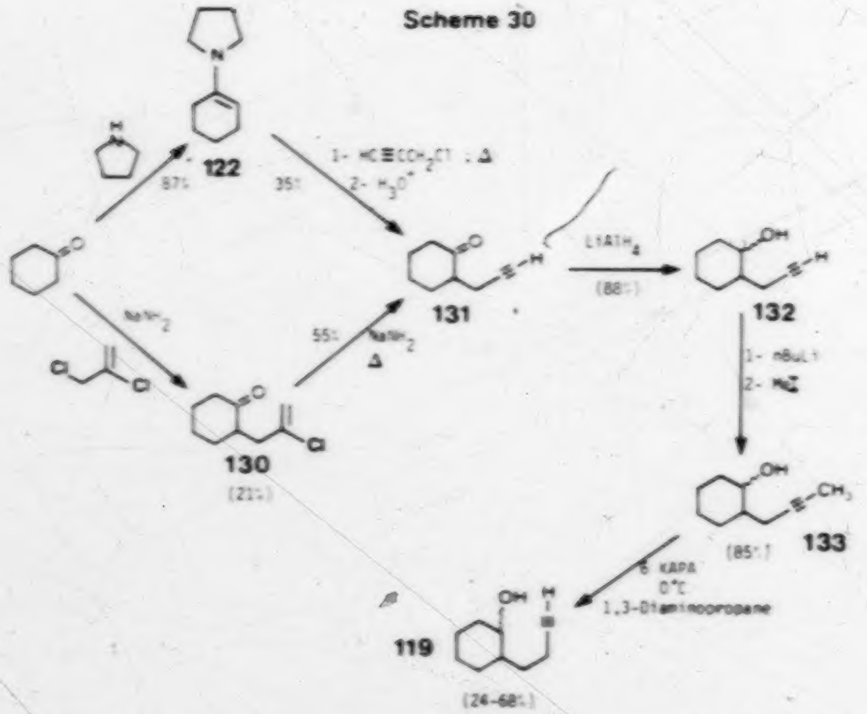
2-(2-Propynyl)cyclohexanone **131** (Scheme 30) was prepared by alkylation of cyclohexanone with 2,3-dichloro-1-propene (21%) followed by dehydrochlorination (55%). Alternatively, alkylation of enamine **122** with 3-chloro-1-propyne gave ketone **131** in 31% overall yield from cyclohexanone. Reduction of the carbonyl group with lithium aluminum hydride produced alcohols **132** (88%) as a 1:1.7 mixture of *cis*- and *trans*-isomers. Double deprotonation and C-alkylation with iodomethane gave methylacetylene **133** (85%) as a 1:2.6 mixture of *cis*- and *trans*-isomers. Base-induced isomerization of the triple bond to the terminal position proved to be difficult. Yields were not reproducible (24-68%) and varied substantially with temperature and reaction time. In the best case, the overall yield of **119** from cyclohexanone was 15.5%.

A more direct approach to *cis*- and *trans*- 2-(3-butynyl)-cyclohexanols **119** was based on a new method[120] for alkylation of epoxides making use of boron acetylides. Here, the correct number of atoms in the side chain is introduced in one step and furthermore, the oxygen functionality is present as a hydroxyl group. This eliminates the

**Scheme 29**

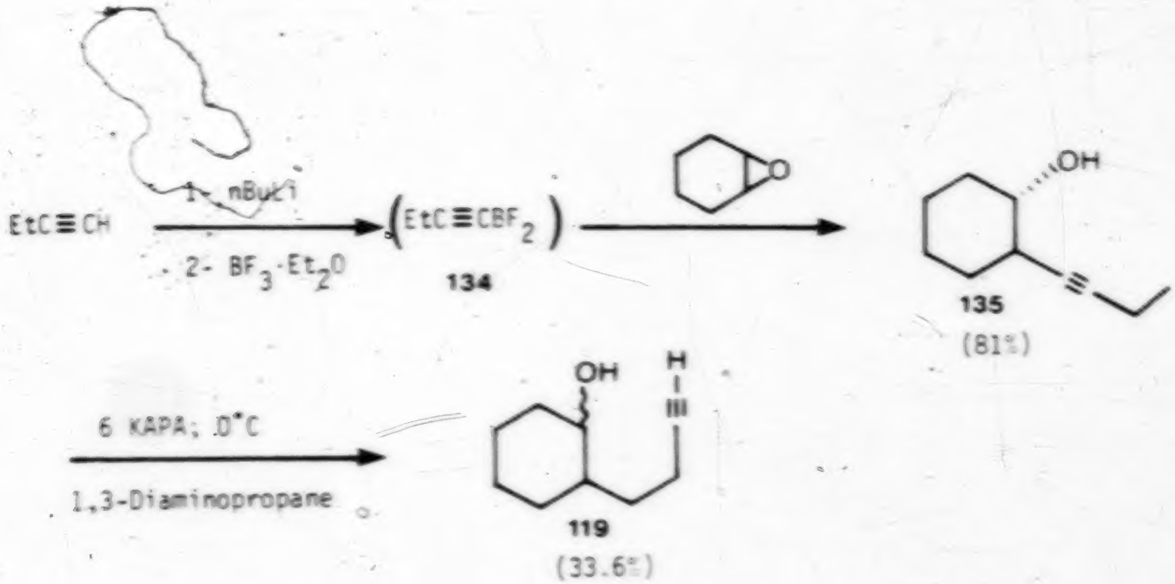

87%
122
59%
Cl
126
72%
OH
Cl
128
61%
OH
119

**Scheme 30**


87%
122
35%
1- HC≡CCH$_2$Cl ; Δ
2- H$_3$O$^+$
131
LiAlH$_4$
(88%)
OH
132
NaNH$_2$
Cl
Cl
130
(21%)
55%
NaNH$_2$
Δ
1- nBuLi
2- MeI
OH
CH$_3$
(85%)
133
6 KAPA
0°C
1,3-Diaminopropane
OH
119
(24-68%)

need for hydride reduction of a carbonyl (Scheme 31).

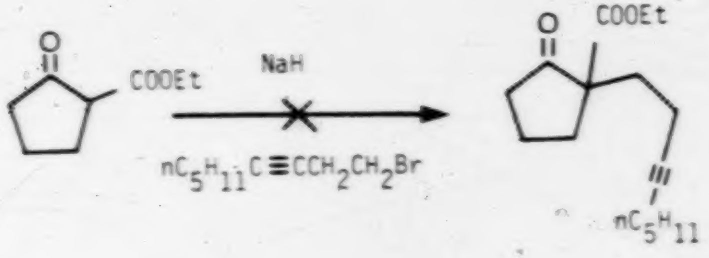
**Scheme 31**



As illustrated in Scheme 31, this procedure would allow conversion of an epoxide in two steps into a substrate properly constituted for radical cyclization. Boron species **134** was generated when 1-butyne was sequentially deprotonated and treated with boron trifluoride etherate. Ring opening of cyclohexene oxide with this reagent gave alcohol **135** (81%). Unfortunately, isomerization of the triple bond to the terminal position could be achieved in 33.6% yield at best and thus provided only a 27.4% overall yield of alcohol **119** from cyclohexene oxide.

Our initial efforts at generating the 2-(3-butynyl)cyclohexyl radical **112** (p. 127) by alkylation technology were not very successful since elaboration of the starting material into a substrate suitable for cyclization, e.g. **119**, required many steps and the overall yield was poor (15 to 27%).

When ketoesters were chosen as substrates for alkylation, the required homopropargylic halides again suffered elimination to enynes (equ. 100).

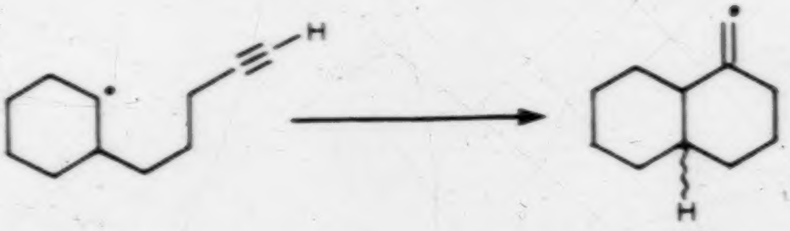


(equ. 100)

Because alkylation procedures that we had tried were not synthetically useful for attaching a 3-butynyl unit α to a carbonyl group, we decided to examine the use of bishomopropargylic halides **136** for generation of 6-heptynyl radicals. The latter can undergo cyclization to a 6-membered ring **137** via a 6-*exo*-closure or a 7-membered ring **138** via an endocyclic pathway (Scheme 32).

To this end, anion **116** of imine **74**, generated by deprotonation with ethylmagnesium bromide, was treated with 5-bromo-1-pentyne. After hydrolysis, ketone **140** was isolated in 49% yield (Scheme 33).

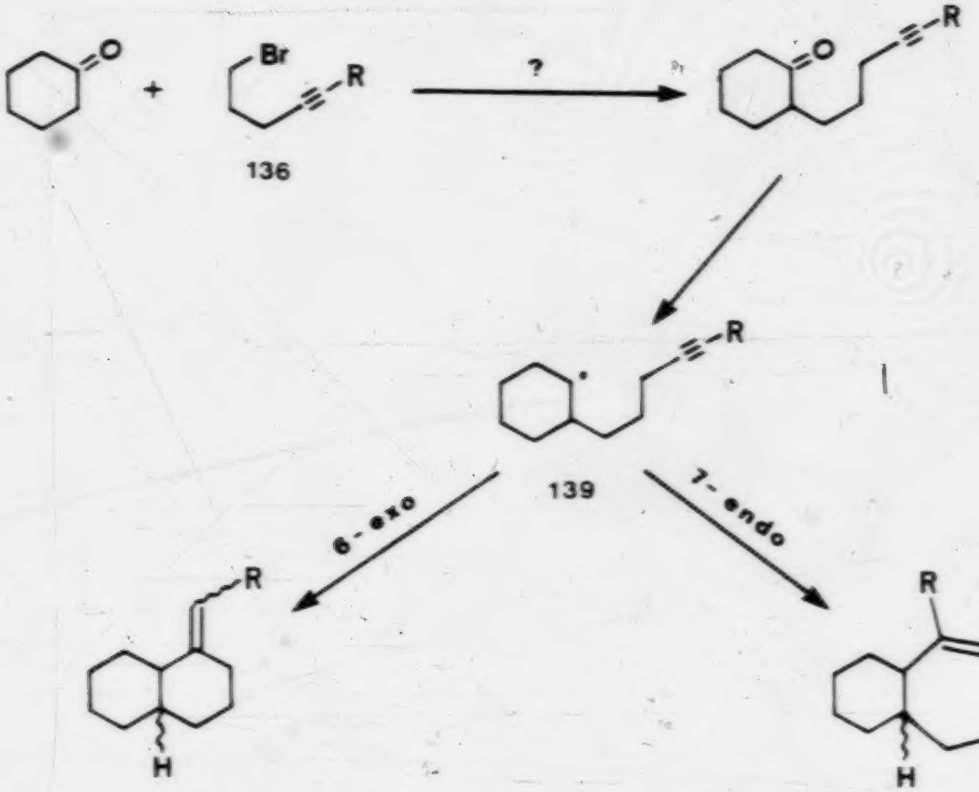
Lithium aluminum hydride reduction of the carbonyl gave alcohol **141** (83%) as a mixture of *cis*- and *trans*- isomers and esterification with 1,1'-thiocarbonylbisimidazole **67** produced ester **142** (74%) also as an isomer mixture. Radical **143** was generated upon homolysis of the carbon-oxygen bond and it underwent cyclization in 24% yield to a *cis* and *trans* mixture of decahydro-1-methylene-naphthalenes **144a** and **144b** in a ratio of 1:2. The two products were identified by comparison with authentic samples prepared as shown in Scheme 34. Unlike previous ring closures, the yield obtained in cyclization of radical **143** was very low (24%). Presumably, the cause lies in the generation of an unstabilized vinyl radical **145** (equ. 101).



**143** **145**

(equ. 101)

Scheme 32


Br
R
?
O
R
R
6- exo
7- endo
R
H
R
H

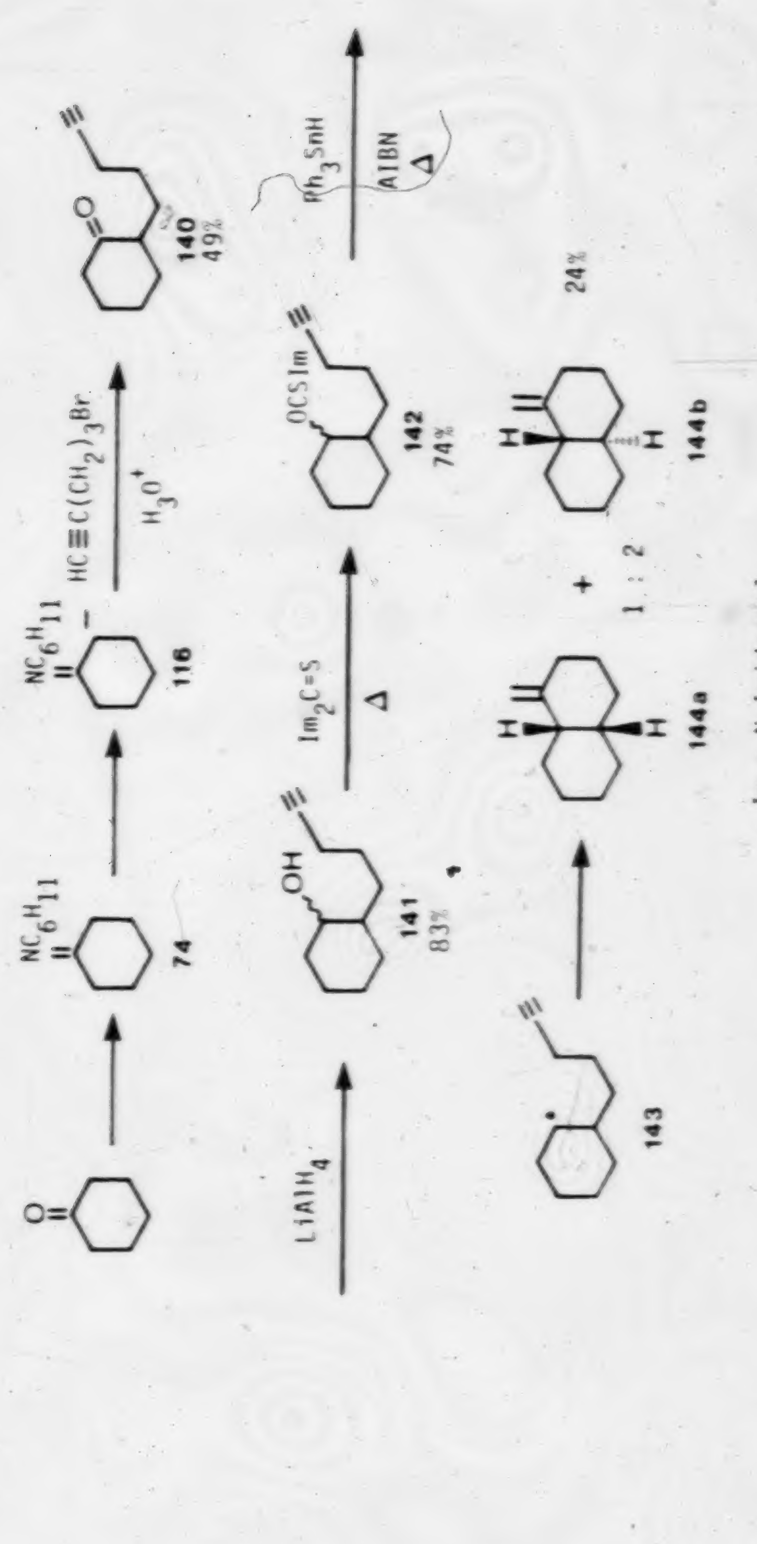
136

139

137

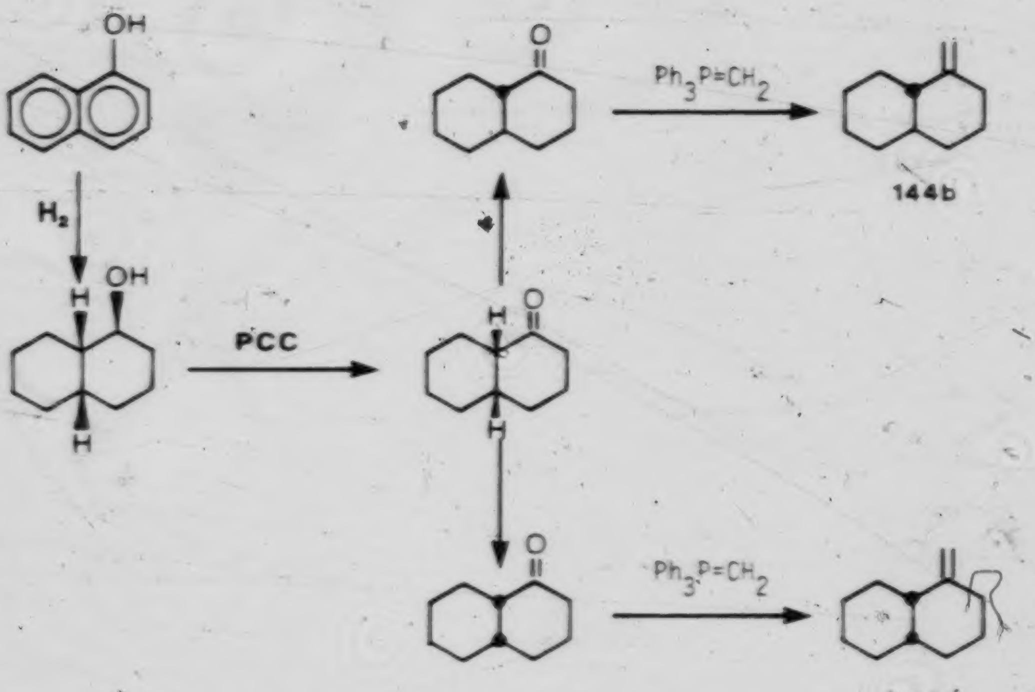
138

**Scheme 33**


74
116
$HC\equiv C(CH_2)_3Br$
$H_3O^+$
140
49%
$LiAlH_4$
141
83%
$Im_2C=S$
Δ
142
74%
$Ph_3SnH$
AIBN
Δ
143
144a
144b
1 : 2
24%

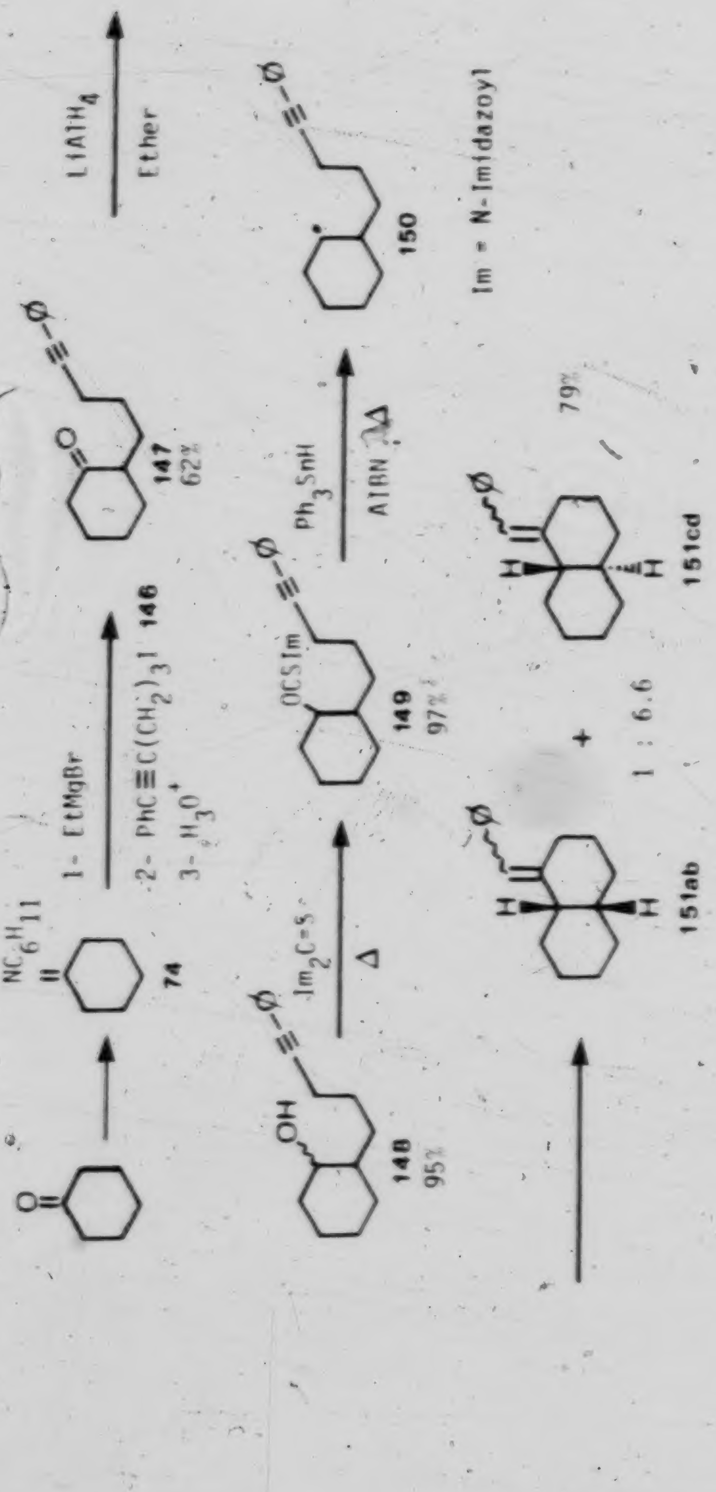
Im = N-Imidazoyl

**Scheme 34**



Substitution of the acetylene side chain at the terminal position by a group that can stabilize radical **145** through delocalization or hyperconjugation with the free spin should increase the yield. To test this hypothesis, alcohol **148**, carrying a strategically located phenyl group was prepared (Scheme 35). Alkylation of cyclohexanone via its imine **74** with iodide **146** gave ketone **147** (62%). After reduction (95%) of the carbonyl group (**147** → **148**) and esterification to the corresponding alkoxythiocarbonylimidazole **149** (97%) (*cis*/*trans* ratio = 1:1.7), treatment with triphenyltin hydride in the presence of AIBN gave radical **150**. Cyclization then produced a mixture of *cis*- and *trans*-alkenes **151ab** and **151cd** in a yield of 79%. Ring closure occurred regiospecifically in a 6-*exo*-fashion. The *cis*-fused decahydro-1-benzylidene-naphthalenes **151ab** were formed as a mixture of

Scheme 35


NC6H11
74
1- EtMgBr
2- PhC≡C(CH2)3I 146
3- H3O+
147
62%
LiAlH4
Ether
OH
148
95%
Im2C=S
Δ
OCSIm
149
97%
Ph3SnH
AIBN, Δ
150
151ab
+
1 : 6.6
151cd
79%

Im = N-Imidazoyl

geometrical isomers (ratio = 1.7). For the *trans*-isomers **151cd**, the ratio was 1:2.5. Alkenes **151ab** and **151cd** were identified by comparison with authentic samples (see Experimental section).

These experiments demonstrate that, like 5-hexenyl radicals, 5-hexynyl and 6-heptynyl radicals undergo ring closure in a regiospecific manner to form cyclic species with an exocyclic double bond. Cyclization of alkyl radicals onto terminal acetylenes proceeds poorly and substitution of the terminal position by an alkyl group or a benzene ring results in an increased yield. When [4.4.0] bicyclic systems are formed by radical closure onto a triple bond, preferential formation of *trans*-fused products is observed.

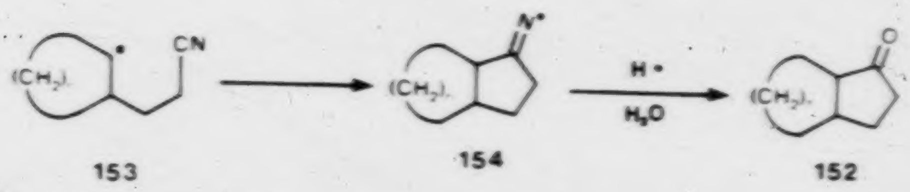
### iii) Conclusion

*exo*-Ring closure of 5-hexynyl and 6-heptynyl radicals provides a method for formation of carbocycles possessing exocyclic double bonds. Elaboration of these products can lead to cyclopentanone and cyclohexanone derivatives. Precursors to 6-heptynyl radicals and acyclic 5-hexynyl radicals are easily accessible by conventional methodology (i.e. alkylation, condensation). However, annulated cyclopentanone derivatives are not available through this route as the required substrates could not be prepared, at least by the methods we tried, involving carbanion chemistry. We decided to investigate an alternative route to cyclopentanones.

## d) Formation of Cyclopentanones by Radical Cyclization onto C≡N Bonds

### i) Introduction

The cyclization of alkyl radicals onto carbon—nitrogen triple bonds has been mentioned briefly in the literature[44] (see Introduction). However, the potential of this reaction as a new synthetic method for formation of cyclopentanones has not been recognized. We felt that iminyl radicals **154**, formed as intermediates in the ring closure process, could lead, after hydrogen abstraction and hydrolysis, to the desired cyclopentanones **152** (equ. 102).



(equ 102)

The elaboration of a simple starting material into a δ-cyano radical such as **153** would provide a general synthesis of cyclopentanone derivatives. Such a process would be a very useful one.

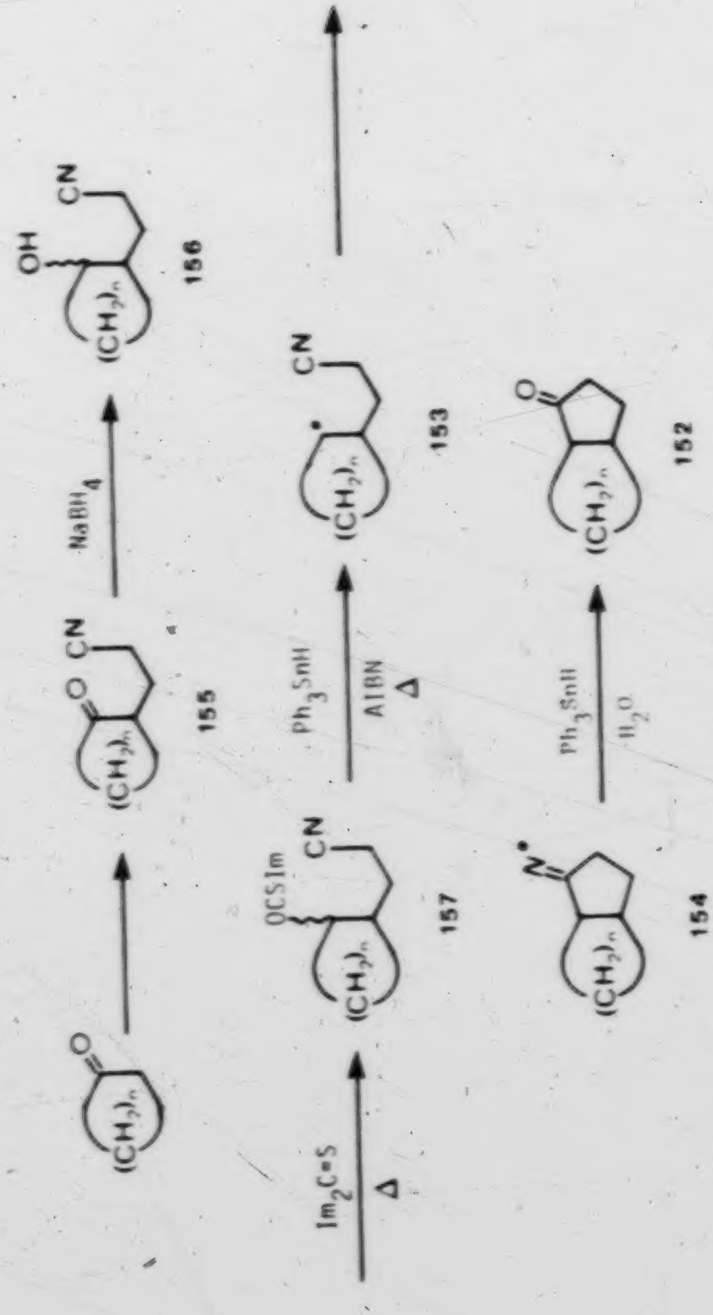
### ii) Results and discussion.

As immediate precursors to δ-cyano radicals **153** we envisaged the possibility of using δ-hydroxynitriles **156** derived from the corresponding ketones **155** as shown in Scheme 36.

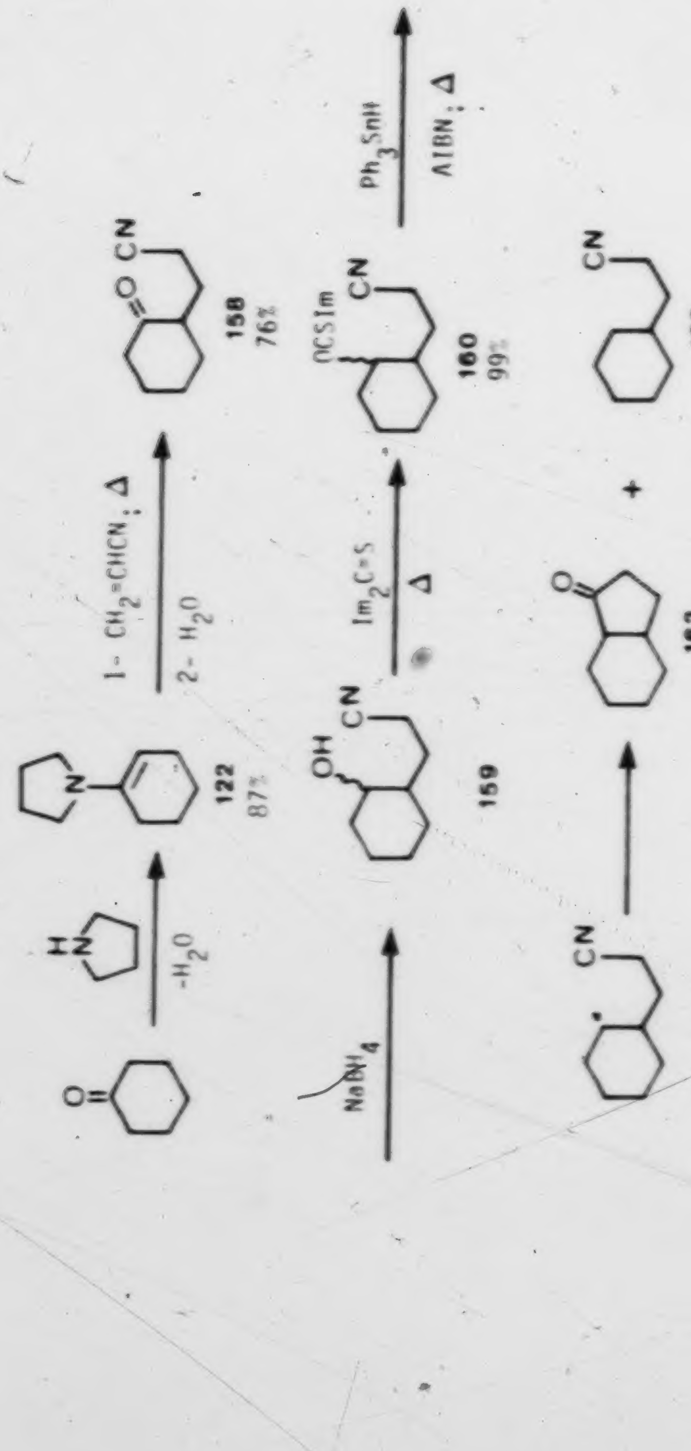
The required δ-ketonitriles such as **155** (n = 0, 1) are known substances, easily prepared by a Michael addition sequence [illegible] and the reduction of the carbonyl group was known to be best effected with sodium borohydride.[illegible] This sequence, as applied to the conversion of cyclohexanone to octahydro-1*H*-inden-1-one **162** is shown in Scheme 37. Michael addition of cyclohexanone–pyrrolidine enamine **122** to acrylonitrile gave δ-keto-nitrile **158** which was reduced and esterified to alkoxythiocarbonylimidazoles **160**. The overall yield for the conversion of cyclohexanone to the cyclization substrate **160** was 65.5% for the 4 steps. Radical **161** was generated in the usual manner and it underwent regiospecific closure to *cis*-fused octahydro-1*H*-inden-1-one **162** (67.7% yield). The structure of bicyclic ketone **162** was determined by comparison of its physical properties with those reported in the literature.[illegible] Cyclohexanepropanenitrile **163** (11%), the product of hydrogen transfer to radical **161**, was also formed. It too was identified in the same fashion. We have carried out a number of experiments of this type and our results are summarized in Table 15 (p. 147).

The Table shows that cycloalkanones are easily transformed into substrates **157** (Scheme **36**) suitable for radical cyclization. In all cases studied, 5-*exo*-closure occurred exclusively. The intermediate imines were hydrolyzed *in situ* to afford the

Scheme 36

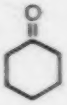
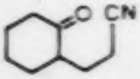
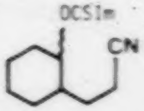
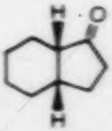
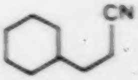
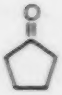
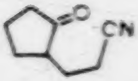
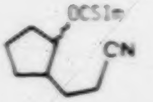
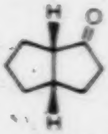
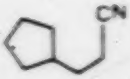
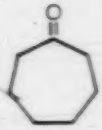
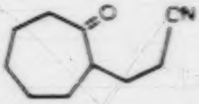
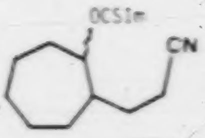
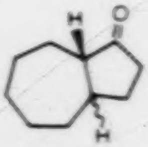
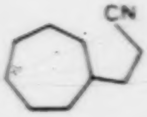
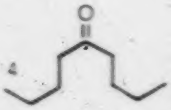
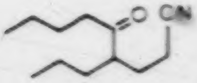
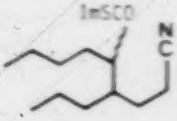
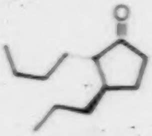
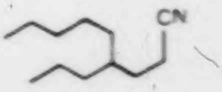
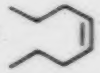
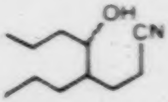
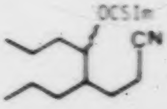
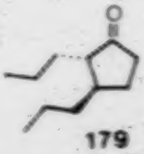
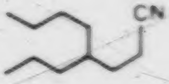

(CH2)n
O
CN
155
NaBH4
OH
156
Im2C=S
Δ
OCSIm
157
Ph3SnH
AIBN
Δ
153
N•
154
Ph3SnH
H2O
152

## Scheme 37



-H$_2$O
122
87%
1- CH$_2$=CHCN; Δ
2- H$_2$O
158
76%
NaBH$_4$
159
Im$_2$C=S
Δ
OCSIm
160
99%
Ph$_3$SnH
AIBN; Δ
161
162
67.7%
+
163
11%

# TABLE 15
# PREPARATION AND CYCLIZATION OF δ-CYANO RADICALS

| ENTRY | STARTING MATERIALS | δ-KETONITRILES[a] (%)[b] | IMIDAZOLIDES (%)[c] | CYCLOPENTANONES (%) | NITRILES (%) |
|---|---|---|---|---|---|
| 1 |  | <br>**158**<br>66% | <br>**160**<br>99% | <br>**162**<br>67.7% | <br>**163**<br>11% |
| 2 |  | <br>**164**<br>54% | <br>**165**<br>78% | <br>**166**<br>18%[d] | <br>**167**<br>21% |
| 3 |  | <br>**168**<br>47% | <br>**169**<br>74% | <br>**170**<br>77%[e] | <br>**171**<br>0% |
| 4 |  | <br>**172**<br>31%[f] | <br>**173**<br>8% | <br>**174**<br>74% | <br>**175**<br>0% |
| 5 | <br>**176** | <br>**177**<br>33%[g] | <br>**178**<br>90% | <br>**179**<br>74% | <br>**180**<br>0% |

Footnotes to Table 15

[a] Prepared via the pyrrolidine enamine. [b] Yield based on starting ketone. [c] Yield based on ketonitrile. Intermediate $\delta$-hydroxynitrile was used without purification. [d] Identified by comparison of physical properties with literature data.[124] [e] Formed as a mixture of isomers in a ratio of 1:2:3:4. [f] Prepared via the morpholine enamine. The material was not pure. [g] Prepared as shown in Scheme 38.

cyclopentanone derivatives. The yields were generally good. An exception is found in entry 2 of Table 15. In this case, the rate of cyclization was sufficiently slow as to allow hyrogen-transfer to the uncyclized radical to become a preferred pathway.

Acyclic ketones (entry 4, Table 15) could not be converted efficiently to the corresponding alkoxythiocarbonylimidazoles via the usual reaction sequence. However, the substrate underwent cyclization in very good yield. Furthermore, the ring closure step gave *trans*-disubstituted cyclopentanone **174** in a completely stereoselective manner.*

Acyclic $\delta$-hydroxynitriles were prepared in better yields using alkenes as starting materials following the procedure[11] shown in Scheme 38 (p. 149).

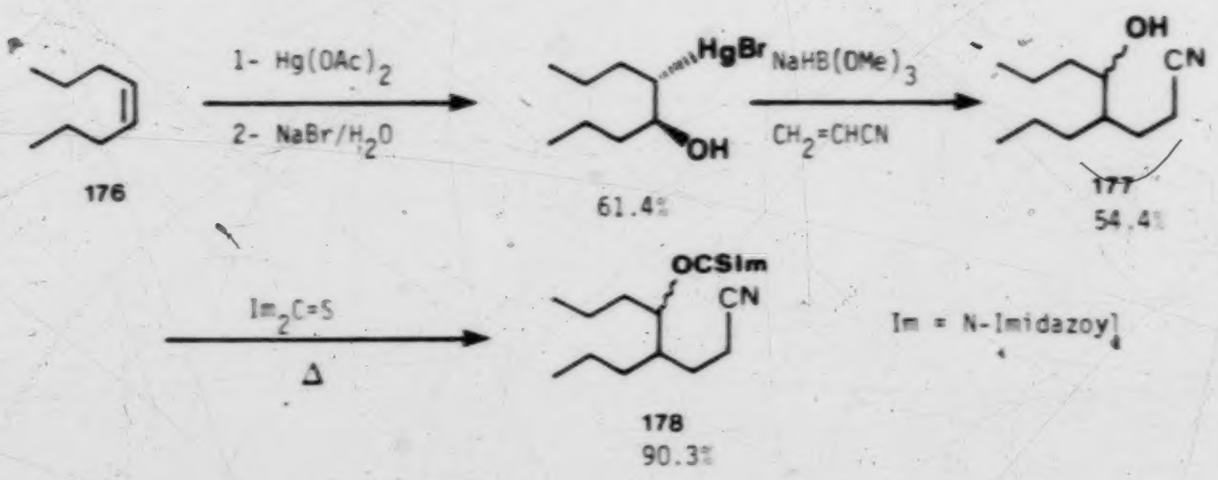
*cis*-4-Octene **176** was hydroxymercurated (61.4%) and homolysis of the carbon–mercury bond using sodium trimethoxyborohydride in the presence of acrylonitrile gave $\delta$-hydroxynitrile **177** (54.4%). Esterification in the usual way (90.3%) followed by radical cyclization produced *trans*-1,2-dipropylcyclopentanone **179** (74%). The relative stereochemistry at the two asymmetric centers was assigned by analogy to the cyclopentanone derivative **174**.

The above experiments show that cyclization of $\delta$-cyanoalkyl radicals occurs regiospecifically in a 5-*exo*- fashion. Hydrolysis of the intermediate imine leads to the corresponding cyclopentanone derivative. The sequence occurs in synthetically acceptable yields and offers an unusual approach to the preparation of 5-membered ring ketones.

---

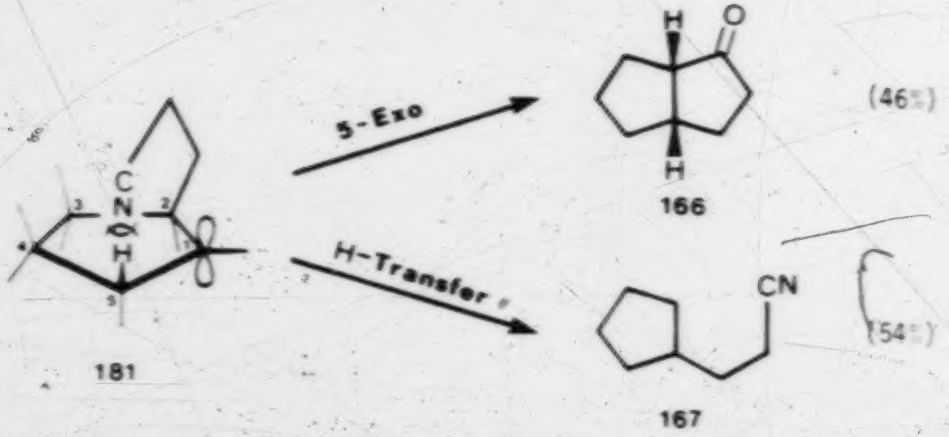
* The relative stereochemistry of the alkyl substituents in cyclopentanone derivative **174** was determined by equilibration studies.[121] After **174** had been refluxed for 24h in 5% ethanolic potassium hydroxyde, the material was recovered unchanged (VPC, $^{13}$C NMR), indicating that the ketone obtained was the thermodynamically more stable one, i.e., with substituents oriented *trans* to each other. In principle, of course, epimerization could have occurred *after* cyclization.

**Scheme 38**


1- Hg(OAc)$_2$
2- NaBr/H$_2$O
HgBr
OH
NaHB(OMe)$_3$
CH$_2$=CHCN
OH
CN
Im$_2$C=S
Δ
OCSIm
CN
Im = N-Imidazoyl
176
61.4%
177
54.4%
178
90.3%

The rate of cyclization of an alkyl radical onto a C≡N is slower than in the case of C=C or C≡C bonds[42]. As a result, products of hydrogen transfer to the intermediate uncyclized radical are also formed in amounts that depend on the particular case. The effect is most dramatic in the cyclization of radical **181** (Fig. 17) to pentalenone derivative **166** In this instance, hydrogen transfer to the intermediate radical **181** is favoured over cyclization. This observation can be explained in terms of an unusually low rate of cyclization due to non-bonded interactions present in the transition state leading to 5-*exo*-ring closure (Fig. 17). For the half-filled *p*-orbital to interact properly with the cyano-group, the side chain must be brought above the plane of the 5-membered ring. In this conformation, non-bonded interactions between the cyano-group and the hydrogen

Figure 17



181

166

167

at C-5 (Fig. 17) become important. Consequently, the activation energy for ring closure increases and the net result is that the rate of cyclization is depressed.

The regiospecificity of the reaction, as was the case for 5-hexenyl and 5-hexynyl radicals, is due to the required arrangement of atoms depicted in Fig. 5 (p. 60). No significant overlap occurs between the half-filled *p*-orbital and the unsaturated system in a transition state leading to *endo*-products (Fig. 18).*

The reaction exhibits a high degree of stereoselectivity. *cis*-Ring fusion geometry is found in both [4.3.0] and [3.3.0] compounds. In the latter case, this is explained by the strained involved in the formation of a *trans*-[3.3.0] system.[illegible] In [4.3.0] systems, *cis*- ring fusion geometry could be the result of epimerization but, we consider, it is more likely to be the consequence of a better overlap between the radical and the cyano-group in the

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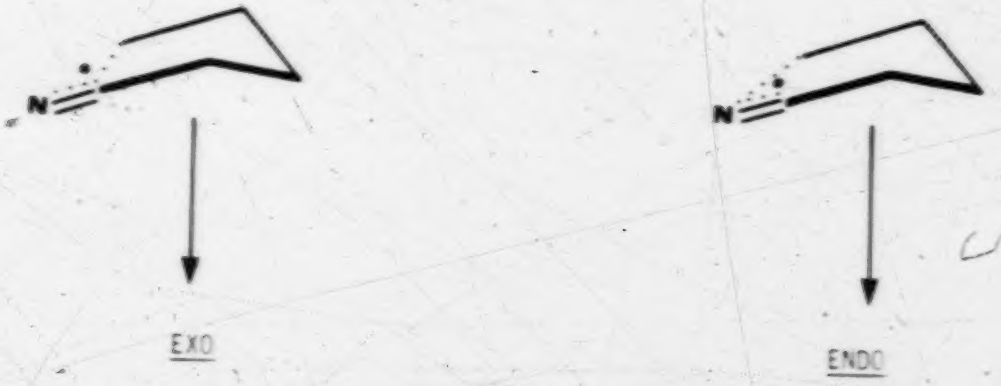
* Other considerations, such as thermochemical factors, are likely to be involved in influencing the regiospecificity of the ring closure since both pathways give rise to products that are structurally very different.

**Figure 18**



transition state leading to *cis*-fused products (Fig. 19).

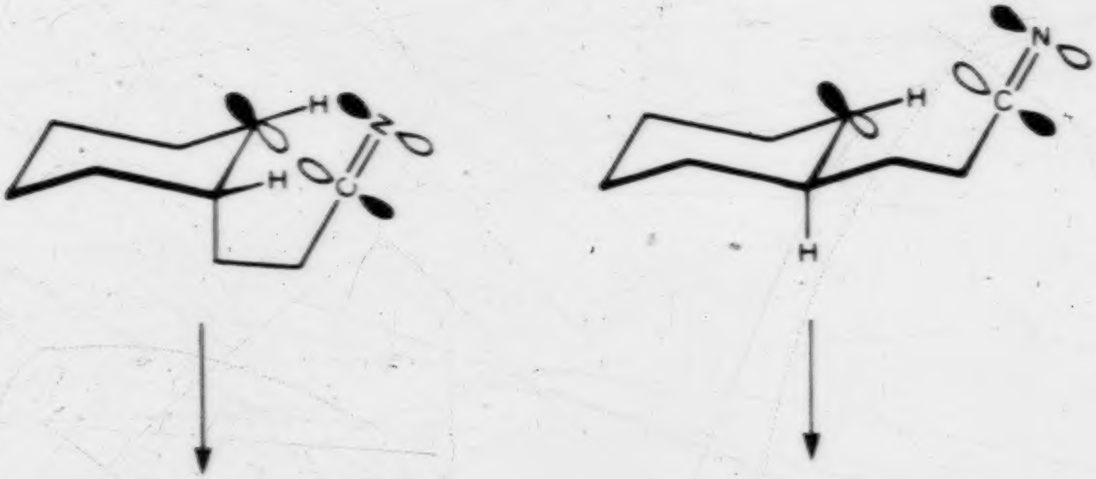
Acyclic δ-cyano-radicals undergo cyclization with complete stereoselectivity. *trans*-1,2-Disubstituted cyclopentanones are formed exclusively. This could be the result of epimerization during work up or a consequence of factors that underlie Beckwith's guidelines. The preferred transition state for cyclization is, presumably, one in which all substituents lie in pseudoequatorial conformations (Fig. 20). This leads to a *trans*-relationship between the substituents in the product. We have not yet sought evidence to distinguish between these possibilities.

### iv) Conclusion:

Cyclopentanone derivatives were prepared by ring closure of δ-cyano radicals. This reaction presents an alternative to the sequence illustrated in Scheme 21 (p. 123) which involved cyclization of a 2-(3-butynyl) radical followed by ozonolysis of the exocyclic double bond to introduce the carbonyl functionality.

The cyclization of radicals onto C≡N occurs regiospecifically via the *exo*-mode. The reaction shows a high degree of stereoselectivity although the mechanistic basis of this has not yet been established.

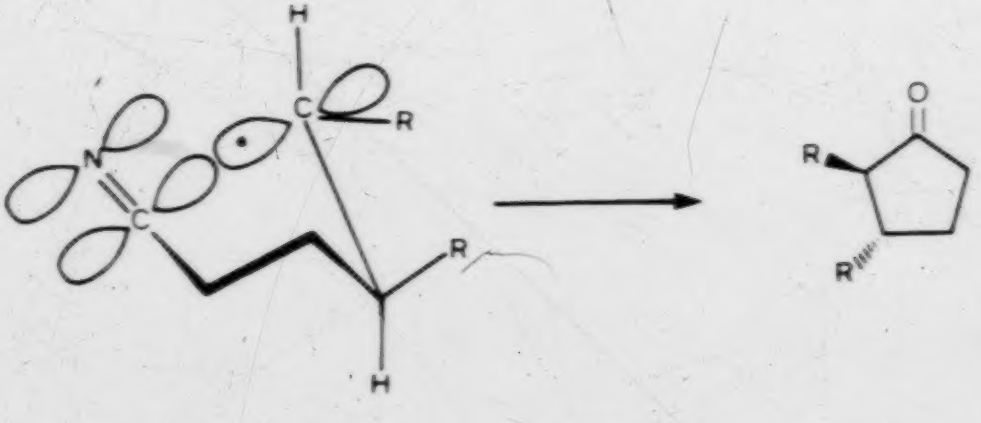
Figure 19



CIS- RING FUSION

TRANS- RING FUSION

Figure 20


H
C
R
N
C
R
H
O
R
R

The intramolecular addition of a radical to a cyano-group is slower than the corresponding attack on carbon–carbon double or triple bonds. As a consequence, factors (such as non-bonded interactions) which retard the process further, can cause side reactions (such as hydrogen transfer to the uncyclized radical) to compete with cyclization. This phenomenon was observed only in the case of [3.3.0] bicyclic systems.

The reaction provides an efficient synthesis of *trans*-1,2-disubstituted cyclopentanones, devoid of any alkylation steps.

**e) Conclusion:**

This work has demonstrated the feasibility of using radical cyclization reactions in a synthetically useful way for the construction of carbocyclic frameworks. The methodology was successfully applied to a variety of substrates including 2-(3-butenyl)-, 2-(3-butynyl)-, 2-(4-pentynyl)- and $\delta$-cyano-radicals. The hydroxyl group was found to be a versatile precursor to the radical site via conversion to thiocarbonylimidazole esters.

The use of 2-(3-butenyl)-radicals leads to a synthesis of cyclopentane derivatives. 5-*Exo*-ring closure occurs regiospecifically in all cases. The degree of stereoselectivity is rather limited except when [4.3.0] and [3.3.0] bicyclic systems are being formed. In those instances, *cis*-ring fusion geometry is observed. The process has the drawback of destroying functionality and preventing further elaboration of the product. For this reason, the cyclization of 2-(3-butynyl)- and 2-(4-pentynyl)-radicals shows more promise as a synthetic method. In both cases *exo*-ring closure occurs. Acetylenic side chains substituted at the terminal position give better yields of cyclized material. The stereoselectivity is comparable to that observed in the alkenyl series.

The cyclization of acetylenic substrates offers the advantage of providing products in which functionality remains available for further manipulations. However, the preparation of the starting materials can present some problems especially in the 2-(3-butynyl)cyclohexyl series (*cf.* dehydrohalogenation of the alkylating agents). The use of this methodology provides access to cyclopentanone derivatives after ozonolysis of the cyclization products.

The same type of compounds can be obtained in a more direct fashion using the carbon–nitrogen triple bond as the intramolecular trap for the alkyl radical. Cyclopentanones are obtained directly after hydrolytic work up. Again, the process is regioselective, showing complete preference for *exo*-closure. The degree of stereoselectivity observed in this series is much higher. The usual preference for the formation of *cis*-fused [4.3.0] and [3.3.0] systems is still present but it extends also to 1,2-disubstituted acyclic $\delta$-cyano radicals. The latter undergo exclusive cyclization to *trans*-1,2-disubstituted cyclopentanones. This high degree of stereoselection brings up the possibility of asymmetric induction in the cyclization of chiral radicals.

We believe that radical ring closures onto triple bonds will prove to be a useful process in organic synthesis.

# III. CONCLUSION

The work described in the second part of this thesis establishes the feasibility of using intramolecular radical cyclizations in a synthetically useful way to prepare cyclic compounds. The technique can be used to make substituted $\gamma$-butyrolactones, a type of compound that has been found to possess anticonvulsant properties of clinical potential.[174]

The basic idea was further extended to the formation of carbocycles. Exploratory work was conducted using 5-hexenyl type radicals which were available by alkylation technology. The hydroxyl group proved to be a convenient precursor to the radical via conversion to its thiocarbonylimidazole ester. Cyclization occurred in a regiospecific fashion to give substituted cyclopentanes. In this type of ring closure functionality is destroyed in the cyclization step and so the products formed are not amenable to further elaboration. For this reason the cyclization of acetylenic substrates was investigated. 5-Hexenyl radicals could not be obtained by conventional alkylation methods but 6-heptynyl radicals were readily available and they underwent regiospecific *exo* closure to 6-membered rings carrying an exocyclic double bond. Terminal acetylenes did not cyclize efficiently but substitution at the terminal carbon led to the desired products in excellent yields. The exocyclic double bond could be manipulated further to give cycloalkanone derivatives after ozonolysis.

Because 5-hexynyl radicals required for the formation of ring fused cyclopentanone derivatives were not easily available, a strategy was developed that would lead directly to the desired products. This was based on the cyclization of $\delta$-cyano radicals. These were accessible via routes involving Michael additions or intermolecular radical additions to acrylonitrile. $\delta$-Cyano radicals underwent regiospecific ring closure to five-membered ring ketones. This new cyclopentanone synthesis should become very useful in organic synthesis because substituted cyclopentanones are produced without need for often problematic alkylation steps. Further work is now in progress to extend the reaction to other systems.

# IV. EXPERIMENTAL

## A. General

See Chapter 1, experimental section (p. 23).

## B. Cyclization of β-(Phenylselenol)esters

**Silver (*E*)-2-butenoate:** (*E*)-2-Butenoic acid (Aldrich, 23.68 g, 0.275 mol) was added to a solution of sodium hydroxide (11.00 g, 0.275 mol) in water (300 mL) and the mixture was stirred at room temperature until formation of the sodium carboxylate was complete (*ca.* 5 min). Silver nitrate (46.71 g, 0.275 mol) in water (75 mL) was added rapidly with stirring, and the white precipitate was collected, washed with water (3 x 25 mL) and acetone (3 x 25 mL), and dried in the dark under oil pump vacuum (*ca.* 12 h). The silver salt (48.00 g, 90.5%) was stored in the dark.

**Silver 2-propenoate:** The procedure for silver (*E*)-2-butenoate was followed using propenoic acid (5.14 g, 0.075 mol), sodium hydroxide (3.00 g, 0.075 mol) in water (15 mL) and silver nitrate (12.75 g, 0.075mol) in water (10 mL). Silver 2-propenoate (13.42 g, 84.1%) was stored in the dark.

**Silver 3-butenoate:** The procedure for silver (*E*)-2-butenoate was followed using 3-butenoic acid (7.32 g, 85 mmol), sodium hydroxide (3.37 g, 84.3 mmol) in water (25 mL) and silver nitrate (14.61 g, 86 mmol) in water (10 mL). Silver 3-butenoate (9.44 g, 58%) was stored in the dark.

**Thallium (*E*)-2-butenoate:** Following a general literature procedure,[126] thallium ethoxide (Aldrich, 6.49 g, 26 mmol) and (*E*)-2-butenoic acid (Aldrich, 2.16 g, 25.1 mmol) in dry ether (20 mL) were stirred overnight at room temperature. The precipitate was collected, washed with ether (2 x 10 mL) and dried under vacuum. The salt[127] (7.11 g, 98%) was obtained as a white solid.

**$\beta$-(Phenylseleno)esters: general procedure**: The alkene in dichloromethane was added to a solution of benzeneselenenyl chloride in the same solvent. After the orange colour had been discharged, dry acetonitrile was added followed by the silver salt of the unsaturated acid. The white slurry was kept overnight in the dark in a sonic bath at room temperature. Suction filtration through Celite (*ca.* 2 x 4 cm) using ether (*ca.* 3 x 20 mL) for washings, and concentration under reduced pressure gave the crude adduct as an orange oil. Flash chromatography over silica gel with 9:1 hexane–ethyl acetate afforded the pure (phenylseleno)ester.

*Trans*–**2–(phenylseleno)-cyclohexanol (*E*)-2–butenoate 26**. The general procedure was followed using benzeneselenenyl chloride (0.59 g, 3.08 mmol) in dichloromethane (5 mL), cyclohexene (0.29 g, 3.5 mmol) in dichloromethane (2 mL), silver (*E*)–2–butenoate (0.67 g, 3.5 mmol), and acetonitrile (20 mL). Flash chromatography over silica gel (2 x 15 cm) gave (phenylseleno)ester **26** (0.77 g, 77%): IR (neat) 1710, 1650, 968 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.25–1.80 (m, 6H), 1.86 (dd, $J$ = 10, 2 Hz, 3H), 2.06–2.24 (m, 2H), 3.27 (ddd, $J$ = 10.4, 9.2, 4.2 Hz, 1H), 4.89 (dt, $J$ = 8.2, 4.2 Hz, 1H), 5.75 (dq, $J$ = 16.8, 1.6 Hz, 1H), 6.88 (dq, $J$ = 16.8, 8.0 Hz, 1H), 7.25 (m, 3H), 7.56 (m, 2H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 17.9, 23.5, 25.7, 31.6, 32.2, 46.2, 75.0, 123.0, 127.5, 128.8, 135.2, 144.4, 165.6; exact mass $m/e$ 324.0630 (calcd for $C_{16}H_{20}O_2Se$ $m/e$ 324.0628). Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24. Found: C, 59.44; 6.19.

*Trans*–**2–(phenylseleno)cyclohexanol (*E*)-2–butenoate 26 from thallium (*E*)-2–butenoate**: Cyclohexene (0.14 g, 1.7 mmol) was added to benzeneselenenyl chloride (0.31 g, 1.62 mmol) in acetonitrile (20 mL). After the orange colour had disappeared, thallium (*E*)–2–butenoate[117] (0.492 g, 1.7 mmol) was added and the mixture was stirred for 24 h at room temperature. After suction filtration through Celite (2 x 4 cm) using ether for washings (3 x 10 mL), the solvent was evaporated and the residue was chromatographed over "normal" silica gel (1 x 15 cm) with 9:1 hexane–ethyl acetate. (Phenylseleno)ester **26** (0.27 g, 51%) was obtained but the material was contaminated with diphenyl diselenide (*ca.* 10%). A pure sample was identical (TLC, IR, $^1$H NMR) to the adduct prepared from the silver salt.

*Trans*–**2–(phenylseleno)cyclopentanol (*E*)-2–butenoate 27**. The general procedure was followed using benzeneselenenyl chloride (2.46 g, 12.84 mmol) in dichloromethane (5 mL), cyclopentene (0.89 g, 13 mmol) in dichloromethane (2 mL), silver (*E*)–2–butenoate (2.70 g, 14 mmol) and acetonitrile (20 mL). Flash chromatography over silica gel (5 × 20 cm) gave (phenylseleno)ester **27** (2.97 g, 75%). IR (neat) 1717, 1655, 972 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.63–1.84 (m, 4H), 1.85 (dd, J = 9, 1.4 Hz, 3H), 2.20 (m, J = 8.0 Hz, 2H), 3.65 (m, 1H), 5.18 (dt, J = 6.3, 3.2 Hz, 1H), 5.74 (dq, J = 15.5, 1.8 Hz, 1H), 6.87 (dq, = 16.0, 7.0 Hz, 1H), 7.24 (m, 3H), 7.56 (m, 2H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ 17.8, 22.5, 30.8, 31.1, 45.9, 81.0, 122.7, 127.3, 128.9, 129.2, 134.0, 144.4, 165.6; exact mass m/e 310.0473 (calcd for $C_{15}H_{18}O_2Se$ m/e 310.0472). Anal. Calcd for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.87. Found: C, 58.30; H, 5.91.

*Trans*–**2–(phenylseleno)cycloheptanol (*E*)-[illegible]–butenoate 28**. The general procedure was followed using benzeneselenenyl chloride (1.35 g, 7.05 mmol) in dichloromethane (5 mL), cycloheptene (0.70 g, 7.3 mmol) in dichloromethane (2 mL), silver (*E*)–2–butenoate (1.45 g, 7.5 mmol) and acetonitrile (20 mL). Flash chromatography over silica gel (2 × 15 cm) gave (phenylseleno)ester **28** (1.81 g, 76%). IR (neat) 1715, 1655, 986 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.40–1.94 (m, 9H), 1.83 (dd, J = 6.5, 1.6 Hz, 3H), 2.13 (m, 1H), 3.47 (ddd, J = 8.2, 7.6, 3.2 Hz, 1H), 5.12 (ddd, J = 7.6, 7.0, 3.4 Hz, 1H), 5.72 (dq, J = 16.0, 2.4 Hz, 1H), 6.87 (dq, J = 16.0, 6.8 Hz, 1H), 7.23 (m, 3H), 7.54 (m, 2H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ 17.9, 22.1, 26.5, 28.2, 31.55, 32.0, 48.8, 77.7, 123.0, 127.5, 128.9, 129.4, 134.8, 144.4, 165.5; exact mass m/e 338.0790 (calcd for $C_{17}H_{22}O_2Se$ m/e 338.0785). Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.58. Found: C, 60.68; H, 6.71.

*Threo*–**5–(phenylseleno)-4–octanol (*E*)-2–butenoate 29**. The general procedure was followed using benzeneselenenyl chloride (3.65 g, 19.06 mmol) in dichloromethane (5 mL), (*Z*)–2–octene (Chemical Samples Co., 2.19 g, 19.3 mmol) in dichloromethane (3 mL), silver (*E*)–2–butenoate (4.44 g, 23 mmol) and acetonitrile (20 mL). Flash chromatography over silica gel (5 × 20 cm) gave (phenylseleno)ester **29** (6.24 g, 93%). IR (neat) 1718, 1657, 970 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.88 (t, J = 6.4 Hz, 3H), 0.91 (t, J = 6.4 Hz, 3H), 1.28 (m, J = 9.0 Hz, 1H), 1.36 (m, J = 8.8 Hz, 1H), 1.46 (m, 1H), 1.60 (m, 2H), 1.70–1.86 (m, 3H), 1.89 (dd, $J$ = 8.8, 1.6 Hz, 3H), 3.28 (ddd, $J$ = 8.6, 5.2, 3.2 Hz, 1H), 5.13 (ddd, $J$ = 8.0, 5.0, 3.2 Hz, 1H), 5.80 (dq, $J$ = 16.0, 1.6 Hz, 1H), 6.40 (dq, $J$ = 16.0, 6.4 Hz, 1H), 7.25 (m, 3H), 7.5 (m, 2H); $^{13}$C NMR ($CDCl_3$, 15.1 MHz) $\delta$ 13.8, 18.0, 19.2, 21.4, 34.0, 34.7, 49.9, 75.8, 122.9, 127.3, 129.1, 130.3, 134.1, 144.8, 166.2; exact mass $m/e$ 354.1096 (calcd for $C_{18}H_{26}O_2Se$ $m/e$ 354.1098). Anal. Calcd for $C_{18}H_{26}O_2Se$: C, 61.18; H, 7.42. Found: C, 61.40; H, 7.45.

*Erythro*-**3-(phenylseleno)-2-butanol (*E*)-2-butenoate 30**. (*E*)-2-butene was bubbled through a solution of benzeneselenenyl chloride (1.90 g, 9.92 mmol) in dichloromethane (20 mL) until the orange solution had been decolorized. The solvent was evaporated under reduced pressure and the residue was dissolved in acetonitrile (20 mL). Silver (*E*)-2-butenoate (2.03 g, 10.5 mmol) was added. The general procedure was then followed. Flash chromatography over silica gel (3 × 15 cm) gave (phenylseleno)ester **30** (2.57 g, 87%): IR (neat) 1720, 1657, 970 cm$^{-1}$; $^1$HNMR ($CDCl_3$, 400 MHz) $\delta$ 1.34 (d, $J$ = 6.0 Hz, 3H), 1.44 (d, $J$ = 7.2 Hz, 3H), 1.84 (dd, $J$ = 0.8, 1.6 Hz, 3H), 3.42 (dq, $J$ = 7.0, 4.8 Hz, 1H), 5.08 (dq, $J$ = 6.4, 4.8 Hz, 1H), 5.72 (dq, $J$ = 16.0, 1.6 Hz, 1H), 6.84 (dq, $J$ = 16.0, 8.0 Hz, 1H), 7.23 (m, 3H), 7.54 (m, 2H); $^{13}$C NMR ($CDCl_3$, 15.1 MHz) $\delta$ 17.8, 17.9, 44.2, 73.2, 94.2, 122.9, 127.7, 129.1, 135.2, 144.6, 165.8; exact mass $m/e$ 298.0474 (calcd for $C_{14}H_{18}O_2Se$ $m/e$ 298.0472). Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.53; H, 6.09.

*Threo*-**3-(phenylseleno)-2-butanol (*E*)-2-butenoate 31**: The procedure employed for ester **30** was followed using (*Z*)-2-butene, benzeneselenenyl chloride (1.74 g, 9.09 mmol) in dichloromethane (20 mL), silver (*E*)-2-butenoate (2.70 g, 14 mmol) and acetonitrile (20 mL). Flash chromatography over silica gel (2 x 15 cm) gave (phenylseleno) ester **31** (2.99 g, 88%): IR (neat) 1720, 1658, 972 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.37 (d, $J$ = 6.4 Hz, 3H), 1.43 (d, $J$ = 6.8 Hz, 3H), 1.87 (dd, $J$ = 8.0, 1.6 Hz, 3H), 1.45 (dq, $J$= 7.0, 4.4 Hz, 1H), 3.50 (dq, $J$= 7.2, 4.6 Hz, 1H), 5.10 (dq, $J$= 6.4, 4.6 Hz, 1H), 5.78 (dq, $J$ = 16.0, 1.6 Hz, 1H), 5.91 (dq, $J$ = 16.0, 7.2 Hz, 1H), 7.24 (m, 3H), 7.55 (m, 2H); $^{13}$C NMR ($CDCl_3$, 15.1 MHz) $\delta$ 16.9, 17.5, 17.9, 43.2, 73.2, 123.0, 127.6, 129.1, 134.6, 144.7, 165.8; exact mass $m/e$ 298.0476 (calcd for $C_{14}H_{18}O_2Se$, $m/e$ 298.0472). Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.54; H, 6.10.

**2-(phenylseleno)ethanol** *(E)*-**2-butenoate 32**: The procedure used for ester **30** was followed using ethylene, benzeneselenenyl chloride (1.27 g, 6.63 mmol) in dichloromethane (20 mL), silver *(E)*-2-butenoate (1.35 g, 7 mmol) and acetonitrile (20 mL). Flash chromatography over silica gel (2 x 15 cm) gave (phenylseleno)ester **32** (0.85 g, 48%). IR(neat) 1720, 1658, 970 cm$^{-1}$; $^1$HNMR (CDCl$_3$, 400 MHz) $\delta$ 1.85 (dd, J= 7.0, 1.7 Hz, 3H), 3.10 (t, J = 7.5 Hz, 2H), 4.35 (t, J = 7.5 Hz, 2H), 5.79(dq, J = 16.0, 1.7 Hz, 1H), 6.93 (dq, J = 16.0, 8.0 Hz, 1H), 7.25 (m, 3H), 7.53 (m, 2H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 18.0, 25.6, 63.5, 122.5, 127.3, 129.2, 133.0, 145.2, 166.2; exact mass, m/e 270.0154 (Calcd for C$_{12}$H$_{14}$O$_2$Se: m/e 270.0159).

*Trans*-**2-(phenylseleno)cyclohexanol propenoate 33**: The general procedure was followed using benzeneselenenyl chloride (0.77 g, 4.02 mmol), cyclohexene (0.36 g, 4.4 mmol) in dichloromethane (5 mL), silver propenoate (0.81 g, 4.5 mmol), and acetonitrile (20 mL). Flash chromatography over silica gel (1.5 x 15 cm) gave (phenylseleno)ester **33** (0.83 g, 67%). IR(neat) 1722, 1639, 1625, 1581 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.27–1.76 (m, 6H), 2.16 (broad t, J = 20 Hz, 2H), 3.26 (ddd, J = 10.1, 9.3, 4.0 Hz, 1H), 4.91 (dt, J = 9.0, 3.7 Hz, 1H), 5.76 (dd, J = 10.6, 2.1 Hz, 1H), 5.99 (dd, J = 17.2, 10.6 Hz, 1H), 6.33 (dd, J = 17.2, 2.1 Hz, 1H), 7.24 (m, 3H), 7.54 (m, 2H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 23.5, 25.7, 31.5, 32.2, 46.0, 75.4, 127.6, 128.7, 128.9, 130.5, 135.2, 165.3; exact mass, m/e 310.0474 (calcd for C$_{15}$H$_{18}$O$_2$Se: m/e 310.0472). Anal. Calcd for C$_{15}$H$_{18}$O$_2$Se: C, 58.25; H, 5.87. Found: C, 58.18; H, 5.70.

*Threo*-**3-(phenylseleno)-2-butanol propenoate 34**: The procedure employed for ester **33** was followed using *(Z)*-2-butene, benzeneselenenyl chloride (0.90 g, 4.7 mmol) in dichloromethane (20 mL), silver propenoate (0.85 g, 5 mmol), and acetonitrile (20 mL). Flash chromatography over silica gel (1.5 x 15 cm) gave (phenylseleno)ester **34** (1.01 g, 76%). IR (neat) 1723, 1637, 1620, 1591 cm$^{-1}$; $^1$HNMR (CDCl$_3$, 100 MHz) $\delta$ 1.30 (d, J = 7.0 Hz, 3H), 1.44 (d, J = 7.0 Hz, 3H), 3.47 (dq, J = 7.0, 4.8 Hz, 1H), 5.13 (dq, J = 6.5, 4.7 Hz, 1H), 5.78 (dd, J = 9.6, 2.6 Hz, 1H), 5.91 (s, 0.25H), 6.09 (s, 0.5H), 6.18 (s, 0.25H), 6.39

(dd, J = 17.0, 2.7 Hz, 1H), 7.27 (m, 3H), 7.58 (m, 2H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ 16.7, 17.3, 42.9, 73.6, 127.6, 128.7, 129.1, 130.7, 134.5, 165.4; exact mass, m/e 284.0317 (calcd for $C_{13}H_{16}O_2Se$, m/e 284.0315). Anal. Calcd for $C_{13}H_{16}O_2Se$: C, 55.13; H, 5.70. Found: C, 53.77; H, 5.56.

***Trans*–2–iodocyclohexanol (*E*)-2–butenoate 35.** Following the literature procedure[illegible] a mixture of cyclohexene (1.32 mL, 13 mmol) and iodine (2.92 g, 11.5 mmol) in benzene (15mL) was added to a suspension of thallium (*E*)–2–butenoate[illegible] (3.36 g, 11.62 mmol) in the same solvent (6 mL). The suspension was stirred for 68 h at room temperature, and filtered by suction through Celite (2 x 4 cm) using ether for washings (3 x 20 mL). The solvent was evaporated and the crude adduct (3.17 g, 94%) was used without further purification. It had IR (neat) 1720, 1655, 971 cm$^{-1}$; $^1$HNMR (CDCl$_3$, 400 MHz) δ 1.24–1.55 (m, 3H), 1.59 (m, 1H), 1.82 (m, 1H), 1.89 (dd, J = 8.2, 1.7 Hz, 3H), 2.03 (m, 1H), 2.14 (m, 1H), 2.43 (m, 1H), 4.10 (ddd, J = 10.4, 9.6, 4.0 Hz, 1H), 4.93 (dt, J = 9.2, 4.0 Hz, 1H), 5.85 (dq, J = 16.0, 1.7 Hz, 1H), 6.01 (dq, J = 16.0, 8.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) δ 18.0, 23.5, 26.9, 31.5, 31.7, 37.7, 76.4, 122.8, 145.2, 165.3; exact mass, m/e 294.0108 (calcd for $C_{10}H_{15}IO_2$, m/e 294.0117). Anal. Calcd for $C_{10}H_{15}IO_2$: C, 40.83; H, 5.14. Found: C, 41.05; H, 5.14.

**General procedure for radical cyclizations:** Oven–dried apparatus and anhydrous solvents were used. A 100–mL round–bottomed flask containing a Teflon–coated magnetic stirring bar and equipped with a reflux condenser fitted with a rubber septum was purged with argon and immersed in an oil bath preheated to 80°C. A benzene solution of the substrate (0.01 – 0.02 M) was injected into the flask and brought to reflux. Benzene solutions of triphenyltin hydride[128] (1.1 – 1.2 equivalents, 0.7 – 0.1 M) and azobisisobutyronitrile (AIBN) (Eastman, 0.05 equivalent, 0.003 M) were then added by syringe simultaneously to the reaction mixture by means of a double syringe pump over a period of 15 h, and refluxing was continued for an arbitrary period of 5 h. The solvent was then removed under reduced pressure and the residue was processed as described for the individual examples.

**Cyclization of (phenylselenol)ester 26: (3α, 3aα, 7aα)– and (3β, 3aα, 7aα)–hexahydro–3–ethyl–2 (3*H*) benzofuranones 40a and 40b:** Following the general procedure, ester **26** (0.707 g, 2.19 mmol) in benzene (100 mL) was cyclized using triphenyltin hydride (0.58 mL, 2.27 mmol) in benzene (10 mL) and AIBN (0.020 g, 0.14 mmol) in benzene (10 mL). After workup, flash chromatography of the residue over silica gel (2 × 15 cm) with 8:2 hexane–ethyl acetate gave a mixture (> 99% pure by VPC) of lactones **40a** and **40b** (0.368 g, 85.3%) in a ratio (VPC) of 1:4. The mixture had IR (neat) 1772 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.01 (isomer **40b**, t, J = 7.7 Hz, 2.35 H), 1.04 (isomer **40a**, t, J = 7.4 Hz, 0.65 H), 1.25 (tq, J = 13.3, 2.8 Hz, 1H), 1.30–1.86 (m, 8H), 2.22 (m, 1H), 2.26 (m, 0.25H), 2.33 (isomer **40b**, ddt, J = 12.6, 6.3, 4.2 Hz, 0.75H), 2.57 (isomer **40b**, ddd, J = 10.1, 5.8, 4.6 Hz, 0.75 H), 4.37 (isomer **40b**, broad q, J = 3.1 Hz, 0.75 H), 4.49 (isomer **40a**, q, J = 5.6 Hz, 0.25 H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ lactone **40a** 11.7, 19.3, 26.7, 28.5, 31.6, 39.4, 47.2; lactone **40b** 12.3, 17.5, 19.8, 22.5, 23.4, 27.6, 37.9, 49.7, 77.4, 179.1; exact mass, m/e 168.1149 (calcd for $C_{10}H_{16}O_2$, m/e 168.1150). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.58; H, 9.77.

**Cyclization of (phenylselenol)ester 27: (3α, 3aα, 6aα)– and (3β, 3aα, 6aα)–hexahydro–3–ethyl–2*H*–cyclopenta[b]furan–2–ones 41a and 41b:**[100] Following the general procedure, ester **27** (0.471 g, 1.523 mmol) in benzene (100 mL) was cyclized using triphenyltin hydride (0.43 mL, 1.67 mmol) in benzene (10 mL) and AIBN (0.0097 g, 0.07 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (2.5 × 15 cm) with 9:1 hexane–ethyl acetate followed by Kugelrohr distillation under vacuum gave a mixture (> 99% pure by VPC) of lactones **41a** and **41b** (0.144 g, 61%) in a ratio (VPC) of 1:2.33. The material had Bp 125–130°C (1.8 mm); lactones **41a** and **41b** had IR (neat) 1765 cm$^{-1}$. Lactone **41a** had $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.03 (t, J = 7.5 Hz, 3H), 1.54–1.98 (m, 7H), 2.04 (broad d, J = 11.0 Hz, 1H), 2.25 (q, J = 4.5 Hz, 1H), 2.60 (m, 1H), 4.94 (dt, J = 5.4, 2.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ 11.5, 23.5, 25.3, 33.5, 33.6, 44.2, 49.2, 84.6, 180.0. Lactone **41b** had $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.04 (t, J = 7.5 Hz, 3H), 1.40–1.84 (m, 5H), 1.86–2.06 (m, 3H), 2.66 (ddd, J = 11.0, 9.0, 5.0 Hz, 1H), 2.81 (broad q, J = 7.0 Hz, 1H), 4.86 (dt, J = 5.3, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ 12.6, 20.0, 24.4, 25.4, 32.7, 43.1, 45.6, 84.5, 178.7. Lactones **41a** and **41b** had exact mass, m/e 154.0993 (calcd for $C_9H_{14}O_2$ m/e 154.0994). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.89; H, 9.26.

**Cyclization of (phenylselenoester 28. (3α, 3aβ, 8aα)-, (3α, 3aα, 8aα)-, (3β, 3aβ, 8aα)- and (3β, 3aα, 8aα)- octahydro-3-ethyl-2*H*-cyclohepta[b]furan-2-ones 42a, 42b, 42c and 42d:** Following the general procedure, ester **28** (0.534 g, 1.58 mmol) in benene (100 mL) was cyclized using triphenyltin hydride (0.40 mL, 1.6 mmol) in benzene (10 mL) and AIBN (0.015 g, 0.1 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (2.5 × 15 cm) with 8:2 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a mixture (> 98% pure by VPC) of lactones **42a**, **42b**, **42c** and **42d** (0.190 g, 66%) in a ratio ($^1$H NMR) of 1:1.8:5:7.9. The material had Bp 160–175°C (2.3 mm). IR (neat) 1770 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.01 (t, J = 7.5 Hz, 2.6 H), 1.08 (t, J = 7.5 Hz, 0.4 H), 1.16–2.06 (m, 1H), 2.20–2.62 (m, 3H), 4.09 (isomer **42c**, dt, J = 10.2, 4.8 Hz, 0.32 H), 4.23 (isomer **42a**, dt, J = 10.2, 4.8 Hz, 0.07 H), 4.55 (isomer **42b**, dt, J = 8.7, 3.3 Hz, 0.13 H), 4.58 (isomer **42d**, dt, J = 9.3, 6.0 Hz, 0.48H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ isomer **42a** 22.8, 24.1, 29.0, 31.7, 33.3, 45.5, 46.3, 84.0; isomer **42b** 21.5, 22.5, 23.0, 25.6, 27.2, 27.3, 47.8, 82.8, 179.2; isomer **42c** 11.0, 21.2, 24.9, 25.4, 27.6, 29.7, 33.1, 48.9, 83.2, 178.4; isomer **42d** 12.3, 18.5, 21.7, 22.1, 28.7, 30.5, 31.0, 43.7, 46.8, 81.6, 178.4; exact mass, m/e 182.1293 (calcd for $C_{11}H_{18}O_2$, m/e 182.1307). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.78; H, 10.14.

**Cyclization of (phenylselenoester 29: (3α, 4β, 5β)-, (3β, 4β, 5β)-, (3α, 4α, 5β)- and (3β-4α-5β)-dihydro-4,5-dipropyl-3-ethyl-2(3*H*)furanones 43a, 43b, 43c and 43d:** Following the general procedure, ester **29** (0.432 g, 1.22 mmol) in benzene (100 mL) was cyclized with triphenyltin hydride (0.33 mL, 1.29 mmol) in benzene (10 mL) and AIBN (0.008 g, 0.05 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (2 × 15 cm) with 97:3 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a mixture (> 99% pure by VPC) of lactones **43a**, **43b**, **43c** and **43d** (0.188 g, 77%) in a ratio (VPC) of 1:9:8:14.5. The material had Bp 126–132°C (1.8 mm). IR (neat) 1770 cm$^{-1}$; $^1$HNMR (CDCl$_3$, 400 MHz): δ 0.84–1.14 (m, 9H, including 0.97 (t, J = 7.5 Hz), 0.99 (t, J = 7.0 Hz), 1.00 (t, J = 7.0 Hz), 1.02 (t, J = 7.1 Hz), 1.06 (t, J = 7.5 Hz), 1.08 (t, J = 7.5 Hz)], 1.15–1.82 (m, 10H), 1.87 (m, 0.50H), 2.14 (m, 0.25H), 2.26 (dt, J = 9.8, 5.3 Hz, 0.5H), 2.45 (m, 0.5H), 2.52 (q, J = 7.5 Hz, 0.25 H), 3.99 (isomer **43d**, dt, J = 8.0, 3.3 Hz, 0.44H), 4.14 (isomer **43c**, dt, J = 7.1, 5.0 Hz, 0.25 H), 4.32 (isomer **43b**, dt, J = 9.5, 4.3 Hz, 0.28H), 4.46 (isomer **43a**, dt, J = 9.0, 5.9 Hz, 0.3 H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) δ isomer **43b** and **43c** 10.8, 12.2, 12.6, 14.1, 14.6, 18.4, 19.0, 19.7, 20.6, 21.1, 26.4, 29.2, 32.7, 36.3, 41.3, 43.2, 43.8, 47.1, 82.6, 82.9, 178.8; isomer **43d** 13.9, 14.3, 19.2, 20.4, 22.7, 35.4, 37.6, 44.7, 47.7, 83.7, 178.7; exact mass, m/e 198.1623 (calcd for $C_{12}H_{22}O_2$, m/e 198.1620). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19. Found: C, 72.83; H, 11.30.

**Cyclization of (phenylselenol)ester 30; (3α, 4β, 5β)-, (3β, 4β, 5β)-, (3α, 4α, 5β)- and (3β, 4α, 5β)- dihydro-4,5-dimethyl-3-ethyl-2(3*H*)furanones 44a, 44b, 44c and 44d:** Following the general procedure, ester **30** (0.447 g, 1.50 mmol) in benzene (50 mL) was cyclized with triphenyltin hydride (0.42 mL, 1.64 mmol) in benzene (10 mL) and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (2 × 15 cm) with 9:1 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a mixture (> 99% pure by VPC) of lactones **44a, 44b, 44c** and **44d** (0.1410 g, 66%) in a ratio (VPC) of 1:6.8:4.4:7.9. The material had Bp 103–106°C (2.0 mm); IR (neat) 1770 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 0.84 (isomer **44b**, d, J = 6.9 Hz, 1H), 1.02 (t, J = 7.5 Hz, 2H), 1.04 (isomer **44c**, d, J = 6.9 Hz, 0.66H), 1.06 (t, J = 7.5 Hz, 1H), 1.14 (isomer **44d**, d, J = 6.8 Hz, 1.19H), 1.24 (isomer **44a**, d, J = 6.8 Hz, 0.15 H), 1.34 (isomer **44b**, d, J = 6.8 Hz, 1.00 H), 1.37 (isomer **44c**, d, J = 6.8 Hz, 0.66 H), 1.40 (isomer **44d**, J = 6.8 Hz, 1.19 H), 1.34–1.60 (m, 0.3*H*), **1.71 (m, 0.82H), 1.84** (isomer **44d**, m, 1.1H), 2.16 (dq, J = 6.0, 6.0 Hz, 0.42H), 2.30 (isomer **44c**, m, 0.27H), 2.37 (isomer **44a**, m, 0.04H), 2.49 (isomer **44b**, m, 0.34H), 2.55 (m, 0.36H), 4.01 (isomer **44d**, dq, J = 9.8, 6.2 Hz, 0.40H), 4.23 (isomer **44c**, dq, J = 6.3, 5.3 Hz, 0.22H), 4.52 (isomer **44b**, dq, J = 6.3, 4.9 Hz, 0.34H), 4.65 (isomer **44a**, dq, J = 6.7, 6.3 Hz, 0.05H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) δ 7.8, 10.9, 11.2, 12.1, 12.4, 12.5, 13.0, 15.5, 16.2, 16.4, 18.3, 18.5, 18.7, 19.3, 19.6, 21.3, 21.7, 36.8, 39.7, 43.3, 44.5, 48.1, 49.2, 77.8, 80.9, 81.5, 178.4, 178.5; exact mass, m/e 142.0993 (calcd for $C_8H_{14}O_2$, m/e 142.0994). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.61; H, 9.90.

**Cyclization of (phenylseleno)ester 31: (3α, 4β, 5β)-, (3β, 4β, 5β)-, (3α, 4α, 5β)- and (3β, 4α, 5β)-dihydro-4,5-dimethyl-3-ethyl-2(3*H*)furanones 44a, 44b, 44c and 44d:** Following the general procedure, ester **31** (0.383 g, 1.29 mmol) in benzene (50 mL) was cyclized with triphenyltin hydride (0.36 mL, 1.4 mmol) in benzene (10 mL) and AIBN (0.005 g, 0.04 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (2 × 15 cm) with 95:5 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a mixture (> 99% pure by VPC) of lactones **44a, 44b, 44c** and **44d** (0.123 g, 67%) in a ratio (VPC) of 1:5.5:4.7:3. The lactone mixture, which had Bp 98–102°C (1.25 mm), was identical (IR, $^1$H NMR, $^{13}$C NMR, VPC, MS) to that prepared from (phenylseleno) ester **30**.

**Cyclization of (phenylseleno)ester 32: 3–ethyldihydro–2(3*H*)furanone 45:** Following the general procedure, ester **32** (0.218 g, 0.81 mmol) in benzene (50 mL) was cyclized using triphenyltin hydride (0.23 mL, 0.9 mmol) in benzene (10 mL) and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (2 × 15 cm) with 9:1 hexane–ethyl acetate and Kugelrohr distillation under reduced pressure gave lactone **45** (0.016 g, 17%) which had Bp 110 – 120°C (10.5mm); IR (neat) 1770 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.01 (t, J = 7.5 Hz, 3H), 1.50 (m, 1H), 1.82–2.00 (m, 2H), 2.38 (m, 1H), 2.48 (dq, J = 9.0, 4.8 Hz, 1H), 4.19(dt, J = 9.0, 6.7 Hz, 1H), 4.35 (m, 1H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ 11.6, 23.4, 28.1, 40.6, 66.4, 182.7; exact mass, m/e 114.0672 (calcd for $C_6H_{10}O_2$, m/e 114.0681).

**Cyclization of (phenylseleno)ester 33: (3α, 3aα, 7aα)– and (3β, 3aα, 7aα)–hexahydro–3–methyl–2(3*H*)benzofuranones 46a and 46b:** Following the general procedure, ester **33** (0.367 g, 1.19 mmol) in benzene (100 mL) was cyclized with triphenyltin hydride (0.33 mL, 1.3 mmol) in benzene (10 mL) and AIBN (0.012 g, 0.08 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (2 x 15 cm) with 9:1 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a mixture (>95% pure by VPC) of lactones **46a** and **46b** (0.044 g, 24%) in a ratio ($^1$HNMR) of 1:3.44. The material had Bp 128 – 135°C (1.4 mm); IR (neat) 1770 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.01 (dq, J = 12.8, 3.7 Hz, 0.7 H), 1.14 (isomer **46b**, d, J = 7.2 Hz, 2.3H), 1.23 (isomer **46a**, d, J = 7.0 Hz, 0.7H), 1.28–1.50 (m, 2H), 1.50–1.98 (m, 5.3H), 2.10–2.33 (m, 2H), 2.44 (isomer **46a**, dq, J = 8.8, 7.2 Hz, 0.25 H), 2.77 (isomer **46b**, dq, J = 7.0, 6.5 Hz, 0.75 H), 4.42 (isomer **46b**, broad q, J = 2.8 Hz, 0.75 H), 4.52 (isomer **46a**, dt, J = 6.3, 7.8 Hz, 0.25 H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) δ isomer **46a** 13.5, 21.2, 21.6, 25.6, 28.8, 38.5, 42.1; isomer **46b** 9.0, 19.8, 23.0, 23.3, 27.6, 39.5, 42.5, 77.4; exact mass, m/e 154.0992 (calcd for $C_9H_{14}O_2$, m/e 154.0994). Anal. Calcd for $C_9H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.61; H, 9.90. The spectral data for lactones **46a** and **46b** were very close to those reported in the literature.[11]

**Cyclization of (phenylselenol)ester 34; (3α, 4β, 5β)-, (3β, 4β, 5β)-, (3β, 4β, 5α)- and (3α, 4β, 5α)-dihydro-3,4,5-trimethyl-2(3*H*)furanones 47a, 47b, 47c and 47d:**[11] Following the general procedure, ester **34** (0.335 g, 1.18 mmol) in benzene (50 mL) was cyclized with triphenyltin hydride (0.3 mL, 1.3 mmol) in benzene (10 mL) and AIBN (0.0055 g, 0.04 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (1.5 x 15 cm) with 9:1 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a mixture (> 99% pure by VPC) of lactones **47a**, **47b**, **47c** and **47d** (0.038 g, 25%) in a ratio (VPC) of 1:6:6:5:7:4. The material had Bp 75–95°C (1.4 mm); IR (neat) 1770 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 0.85 (isomer **47b**, d, J = 7.5 Hz, 1.0H), 1.02 (isomer **47c**, d, J = 7.3 Hz, 0.75H), 1.07 (isomer **47a**, d, J = 7.0 Hz, 0.15H), 1.12 (isomer **47d**, d, J = 6.8 Hz, 1.11H), 1.15 (isomer **47c**, d, J = 7.8 Hz, 0.75H), 1.16 (isomer **47b**, d, J = 7.3 Hz, 1.0H), 1.22 (isomer **47d**, d, J = 7.1 Hz, 1.11H), 1.33 (isomer **47b**, d, J = 6.8 Hz, 1.00H), 1.37 (isomer **47c**, d, J = 7.1 Hz, 0.75H), 1.38 (isomer **47a**, d, J = 7.0 Hz, 0.15H), 1.39 (isomer **47d**, d, J = 7.5 Hz, 1.11H), 1.50–1.90 (m, 1H), 2.22 (isomer **47d**, m, 0.37H), 2.34 (isomer **47a**, q, J = 6.8 Hz, 0.05H), 2.49 (m, 0.3H), 2.75 (isomer **47c**, q, J = 7.7 Hz, 0.25H), 2.83 (isomer **47b**, q, J = 7.6 Hz, 0.33H), 4.04 (isomer **47d**, dq, J = 9.6, 6.4 Hz, 0.37 H), 4.22 (isomer **47c**, q, J = 6.4 Hz, 0.25 H), 4.56 (isomer **47b**, dq, J = 6.4, 4.8 Hz, 0.33 H), 4.68 (isomer **47a**, dq, J = 7.2, 6.4 Hz, 0.05 H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz, spectrum run on mixture) δ isomer **47a** 13.4, 18.6, 44.0, 47.8, 80.3, 177.9; isomer **47b** 8.3, 10.0, 14.6, 40.8, 46.5, 77.7, 179.2; isomer **47c** 10.2, 12.6, 19.1, 38.2, 40.4, 81.3, 179.6; isomer **47d** 13.0, 15.5, 18.5, 38.0, 43.2, 81.1, 178.7; exact mass, m/e 128.0833 (calcd for $C_7H_{12}O_2$, m/e 128.0837). The lactones had spectral characteristics extremely close to those reported in the literature.[99]

**Cyclization of iodoester 35: (3α, 3aα, 7aα)– and (3β, 3aα, 7aα)–hexahydro–3–ethyl–2(3*H*)benzofuranones 40a and 40b:** Following the general procedure, iodide **35** (0.633 g, 2.15 mmol) in benzene (100mL) was cyclized with triphenyltin hydride (0.6 mL, 2.37 mmol) in benzene (10 mL) and AIBN (0.006 g, 0.04 mmol) in benzene (10 mL). After workup, the residue was dissolved in ether (50 mL) and stirred with saturated aqueous potassium fluoride (25 mL) for 30 min. The mixture was extracted with ether (2 x 20 mL) and the solution was dried ($MgSO_4$) and evaporated. Flash chromatography over silica gel (1.5 x 15 cm) with 8:2 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a mixture (> 98% pure by VPC) of lactones **40a** and **40b** (0.205 g, 56.7%) in a ratio ($^1$H NMR) of 1:4. The compounds, examined as a mixture, were identical (TLC, VPC, IR, $^1$H NMR) to those prepared from (phenylseleno)ester **26**.

**α–Ethyl–1–hydroxy–cyclopentaneacetic acid, 48:**[129] Following the literature procedure,[129] 2–bromobutanoic acid (15 g, 0.09 mol) was converted into its tetrahydropyranyl [illegible], which was then mixed with cyclopentanone (5.4 mL, 0.06 mol) and treated with zinc dust (6.45 g, 0.099 mol) in THF (90 mL), to give after acidic workup, hydroxy–acid **48**. The material was used without further purification to prepare authentic lactones **41a** and **41b**. The crude hydroxy–acid **48** had $^1$H NMR ($CDCl_3$, 80 MHz) δ 1.00 (t, J = 8.0 Hz, 3H), 1.30–2.25 (m, 10H), 2.37 (dd, J = 8.5, 6.0 Hz, 1H), 7.20 (broad s, 2H).

**Authentic (3α, 3aα, 6aα)– and (3β, 3aα, 6aα)–hexahydro–3–ethyl–2*H*–cyclopenta[b]furan–2–ones 41a and 41b:**[100] Following the literature procedure,[100] concentrated (98%) sulfuric acid (0.7 mL) was added to a solution of hydroxy acid **48** (4.43 g, 25.7 mmol) in benzene (50mL). The mixture was refluxed for 18 h and cooled. Water (25 mL) was added, the organic phase was separated, dried ($Na_2SO_4$) and evaporated. The residue was distilled under vacuum to give a mixture of lactones **41a** and **41b** (2.46 g, 62%), Bp 125–130°C (1.9 mm) in a ratio (VPC) of 1:1.1. The lactones (examined as a mixture) were identical (TLC, VPC, $^1$H NMR, $^{13}$C NMR) to those prepared by our cyclization route. The isomers were separated by preparative VPC on Carbowax 20M at 160°C. (3α, 3aα, 6a$\alpha$)-Hexahydro-3-ethyl-2*H*-cyclopenta[b]furan-2-one **41a** (97% pure by VPC) had $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.03 (t, J = 7.5 Hz, 3H), 1.54-1.98 (m, 7H), 2.04 (broad d, J = 11.0 Hz, 1H), 2.25 (q, J = 4.5 Hz, 1H), 2.60 (m, 1H), 4.94 (dt, J = 5.4, 2.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ 11.5, 23.5, 25.3, 33.5, 33.6, 44.2, 49.2, 84.6, 180.0. (3$\beta$, 3a$\alpha$, 6a$\alpha$)-Hexahydro-3-ethyl-2*H*-cyclopenta[b]furan-2-one **41b** (95% pure by VPC) had $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.04 (t, J = 7.5 Hz, 3H), 1.40-1.84 (m, 5H), 1.86-2.06 (m, 3H), 2.66 (ddd, J = 11.0, 9.0, 5.0 Hz, 1H), 2.81 (broad q, J = 7.0 Hz, 1H), 4.86 (dt, J = 5.3, 1.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 12.6, 20.0, 24.4, 25.4, 32.7, 43.1, 45.6, 84.5, 178.7.

**Equilibration studies of lactones 41a and 41b**: The lactones (0.050 g, 0.32 mmol) were dissolved in separate batches of decahydronaphthalene (tetralin, 10 mL). Anhydrous potassium hydrogen carbonate (0.100 g, 1.0 mmol) was added to each solution and the mixtures were refluxed for 30 min. The supernatant solutions were analyzed by VPC on a DEGS column (6 ft) at 200°C. Lactones **41a** and **41b** were found to isomerize to the same equilibrium mixture containing **41a** and **41b** in a ratio of *ca.* 1:0.33.

| Initial ratio<br>**41a**:**41b** | Equilibrium ratio<br>**41a**:**41b** |
|---|---|
| 1:2.3 | 1:0.35 |
| 1:0.29 | 1:0.30 |
| 1:2.5 | 1:0.33 |

**Tetrahydro-4-methyl-2*H*-pyran-2-one 52**:[130] 3-Methylglutaric anhydride [6.40 g, 0.05 mol, Bp 114.5 - 115.5°C (2.5 mm)[131]] was reduced with lithium aluminum hydride (1.10 g, 0.029 mol) in dry THF (100 mL) at -60°C as described in the literature.[130] After 110 min at 0°C, the reaction mixture was hydrolyzed with 50% aqueous HCl (20 mL) at -30°C. The product was extracted with ether (3 x 20 mL) and the extracts were dried (MgSO$_4$) and concentrated. Flash chromatography over silica gel (2 x 15 cm) with 7:4

hexane–ethyl acetate and Kugelrohr distillation under reduced pressure (Bp 122–132°C (12 mm)[135]) gave material that was further purified by flash chromatography over silica gel (2 × 15 cm) with 2:1 dichloromethane–ethyl acetate. Lactone **52** was obtained in *ca.* 5% yield and had IR (neat) 1735 $cm^{-1}$; $^1H$NMR ($CDCl_3$, 400 MHz) δ 1.06 (d, J = 6.4 Hz, 3H), 1.56 (m, 1H), 1.94 (m, 1H), 2.10 (m, 1H), 2.14 (t, J = 9.6 Hz, 1H), 2.68 (dq, J = 11.7, 1.9 Hz, 1H), 4.28 (ddd, J = 11.6, 10.4, 3.8 Hz, 1H), 4.42 (ddd, J = 11.6, 4.8, 3.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) δ 21.5, 26.6, 30.7, 38.3, 68.6, 171.3.

**Tetrahydro-4-methyl-3-(phenylseleno)-2*H*-pyran-2-one (50):** Lithium diisopropylamide (1.1 mmol) was prepared at −70°C by addition of *n*-butyllithium (1.29 M in hexane, 0.85 mL, 1.1 mmol) to a solution of diisopropylamine (0.15 mL, 1.1 mmol) in THF (10 mL). The mixture was kept at −70°C for 5 min and lactone **52** (0.114 g, 1 mmol) in dry THF (2 mL + 1 mL rinse) was added. The mixture was stirred for 1 h at −70°C. Benzeneselenenyl chloride (0.192 g, 1 mmol) in THF (2 mL + 1 mL rinse) was injected at −70°C into the stirred solution and after 15 min saturated aqueous ammonium chloride (25mL) was added. The mixture was extracted with ether (3 × 20 mL) and the combined extracts were washed with saturated aqueous sodium chloride (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of crude lactone **50** over silica gel (1 × 15 cm) with 7:4 hexane–ethyl acetate gave pure material (0.112 g, 42%) as a 1:14 mixture ($^1H$ NMR) of isomers: IR ($CCl_4$) 1734, 1579 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.21 (major isomer, d, J = 7.5 Hz, 2.8H), 1.24 (minor isomer, d, J = 6.8 Hz, 0.2H), 1.54 (ddq, J = 9.7, 4.5, 4.5 Hz, 1H), 1.98 (dddd, J = 14.6, 7.5, 5.3, 5.3 Hz, 1H), 2.20 (m, 1H), 3.52 (d, J = 6.0 Hz, 1H), 4.17 (major isomer, ddd, J = 12.5, 10.0, 3.5 Hz, 0.9H), 4.34 (major isomer, dt, J = 11.0, 4.2 Hz, 0.9H), 4.47 (minor isomer, ddd, J = 11.5, 6.0, 4.0 Hz, 0.1H), 7.34 (m, 3H), 7.58 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) δ major isomer 21.1, 29.7, 33.7, 46.3, 67.4, 128.9, 129.2, 135.6, 170.5, minor isomer 19.2, 27.9, 30.8, 49.7, 68.3; exact mass, m/e 270.0154 (calcd for $C_{12}H_{14}O_2Se$, m/e 270.0159).

**Action of triphenyltin hydride on lactone 50:** Following the general procedure for cyclizations (see p. 161), lactone **50** (0.098 g, 0.364 mmol) in benzene (50 mL) was treated with triphenyltin hydride (0.1mL, 0.4 mmol) in benzene (10 mL) and AIBN (0.007 g, 0.05 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (1 x 15 cm) with 7:3 hexane–ethyl acetate and Kugelrohr distillation under vacuum gave a single lactone (0.027 g, 64%) identified as 4–methyltetrahydro–2*H*–pyran–2–one **52** on the basis of its spectral properties (IR, $^1$H NMR, $^{13}$C NMR) and a comparison with an authentic sample.[131] The present material had Bp 100–105°C (0.8 mm); IR (CDCl$_3$) 1730 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.08 (d, $J$ = 6.5 Hz, 3H), 1.56 (m, 1H), 1.96 (m, 1H), 2.10 (m, 1H), 2.14 (t, $J$ = 9.5 Hz, 1H), 2.70 (dq, $J$ = 11.5, 2.0 Hz, 1H), 4.30 (ddd, $J$ = 11.6, 10.4, 3.8 Hz), 4.44 (ddd, $J$ = 11.5, 4.8, 3.7 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 21.2, 26.4, 30.5, 38.1, 68.3, 171.0; exact mass, m/e 114.0680 (calcd for $C_6H_{10}O_2$, m/e 114.0681).

*Trans*–*N*–**[2–(phenylseleno)cyclohexyl]–**(*E*)**-2–butenamide 63**: Based on a procedure described in the literature,[111] cyclohexene (0.42 g, 5 mmol), benzeneselenenyl chloride (0.96 g, 5 mmol), 2–butenenitrile[112] (5 mL), trifluoromethane sulfonic acid (0.75 g, 5 mmol) and water (0.45mL, 25 mmol) were mixed in that order. After aqueous workup the crude material was purified by flash chromatography over silica gel (1.5 x 5 cm) with 7:4 hexane–ethyl acetate to give (phenylseleno)amide **63** (0.89 g, 55.3%) as a white solid. IR (CDCl$_3$) 3430, 3310, 1675, 1638, 963 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 100 MHz) $\delta$ 1.00–2.38 (m, 8H), 1.83 (dd, $J$ = 7.0, 1.7 Hz, 3H), 3.06 (dt, $J$ = 11.0, 4.2 Hz, 1H), 3.86 (broad m, 1H), 5.66 (broad s, 1H), 5.71 (dq, $J$ = 15.0, 2.0 Hz, 1H), 6.79 (dq, $J$ = 15.0, 7.0 Hz, 1H), 7.25 (m, 3H), 7.54 (m, 2H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 17.6, 24.5, 26.6, 33.8, 47.8, 52.9, 125.3, 127.6, 128.1, 128.9, 135.4, 139.5, 165.1; exact mass, m/e 323.0793 (calcd for $C_{16}H_{21}NOSe$, m/e 323.0788). Anal. Calcd for $C_{16}H_{21}NOSe$: C, 59.62; H, 6.57; N, 4.35. Found: C, 59.47; H, 6.66; N, 4.48.

*Threo*–*N*–**[3–phenylseleno)2–butyl]–**(*E*)**-2–butenamide 64**: Based on a procedure described in the literature,[111] (*Z*)–2–butene was bubbled through a solution of benzeneselenenyl chloride (1.02 g, 5.33 mmol) in 2–butenenitrile[112] (3 mL) until the colour had been discharged. Trifluoromethane sulfonic acid (0.80 g, 5.33 mmol) and water (0.48 mL, 26.6 mmol) were added sequentially and the mixture was refluxed for 1 h and cooled. The black solution was poured into saturated aqueous NaHCO$_3$ (30 mL) and the mixture was extracted with chloroform (2 x 20 mL). The extract was washed with saturated aqueous sodium chloride, dried ($MgSO_4$) and was evaporated. Flash chromatography over silica gel (1.5 x 5 cm) with 9:1 hexane–ethyl acetate to remove diphenyl diselenide and then with 1:1 hexane–ethyl acetate to elute the product, followed by recrystallization from 5:1 hexane–ethyl acetate gave pure (phenylseleno)amide **64** (0.57 g, 36%): IR ($CDCl_3$) 3438, 3320, 1676, 1638, 963 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 100 MHz) $\delta$ 1.22 (d, J = 7.0 Hz, 3H), 1.41 (d, J = 7.0 Hz, 3H), 1.85 (dd, J = 7.0, 1.7 Hz, 3H), 3.53 (dq, J = 17.5, 7.5 Hz, 1H), 4.35 (m, 1H), 5.69 (broad s, 1H), 5.76 (dq, J = 15.0, 1.6 Hz, 1H), 6.82 (dq, J = 15.0, 7.0 Hz, 1H), 7.30 (m, 3H), 7.58 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 17.6, 18.7, 18.9, 45.2, 49.5, 125.2, 127.5, 129.1, 134.5, 139.8, 165.4; exact mass, m/e 297.0633 (calcd for $C_{14}H_{19}NOSe$, m/e 297.0632). Anal. Calcd for $C_{14}H_{19}NOSe$: C, 56.75; H, 6.46; N, 4.73. Found: C, 56.54; H, 6.49; N, 4.72.

**Attempted cyclization of (phenylseleno)amide 63; *N*-cyclohexyl-(*E*)-2-buteneamide 65**: Following the general procedure (see p. 161) amide **63** (0.107 g, 0.33 mmol) in benzene (50 mL) was treated with triphenyltin hydride (0.10 mL, 0.38 mmol) in benzene (10 mL) and AIBN (0.012 g, 0.08 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (1.5 x 15 cm) with 7:3 hexane–ethyl acetate gave a single product (0.049 g, 87%) as a white solid which was identified as amide **65** based on its spectral properties: IR ($CDCl_3$) 3438, 3310, 1673, 1633, 966 cm$^{-1}$; $^1H$NMR ($CDCl_3$, 400 MHz) $\delta$ 1.17 (dq, J = 12.0, 3.0 Hz, 3H), 1.40 (tq, J = 12.6, 3.6 Hz, 2H), 1.65 (td, J = 12.7, 3.6 Hz, 1H), 1.72 (td, J = 13.2, 3.6 Hz, 2H), 1.87 (dd, J = 7.2, 1.7 Hz, 3H), 1.98 (qd, J = 12.6, 3.0 Hz, 2H), 3.86 (m, 1H), 5.43 (broad s, 1H), 5.79 (dq, J = 15.2, 1.7 Hz, 1H), 6.84 (dq, J = 15.2, 6.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 17.6, 24.9, 25.6, 33.3, 48.0, 125.6, 139.3, 165.0; exact mass, m/e 167.1308 (calcd for $C_{10}H_{17}NO$, m/e 167.1310).

**Attempted cyclization using (phenylseleno)amide 64; *N*-2-butyl-(*E*)-2-buteneamide 66**: Following the general procedure (see p. 161), (phenylseleno)amide **64** (0.102 g, 0.34 mmol) in benzene (100 mL) was treated with triphenyltin hydride (0.10 mL, 0.4 mmol) in benzene (10 mL) and AIBN (0.006 g, 0.04 mmol) in benzene (10 mL). After workup, flash chromatography over silica gel (1.5 x 15 cm) with 1:1 hexane–ethyl acetate gave a single product (0.037 g, 76%) as a white solid which was identified as amide **66**

based on its spectral properties. IR ($CDCl_3$) 3439, 3310, 1675, 1635, 966 $cm^{-1}$; $^1H$NMR ($CDCl_3$, 100 MHz) $\delta$ 0.91 (t, J = 7.0 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.50 (q, J = 7.0 Hz, 2H), 1.86 (dd, J = 7.0, 2.0 Hz, 3H), 3.98 (tq, J = 9.3, 6.0 Hz, 1H), 5.52 (broad s, 1H), 5.81 (dq, J = 15.0, 2.0 Hz, 1H), 6.82 (dq, J = 15.0, 7.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 10.3, 17.5, 20.4, 29.7, 46.4, 125.5, 139.1, 165.3; exact mass m/e 141.1151 (calcd for $C_8H_{15}NO$ m/e 141.1154).

**1-(1-Cyclohexen-1-yl)pyrrolidine 122:**[133] The literature procedure[133] was followed. A solution of cyclohexanone (73.00 g, 0.744 mol) and pyrrolidine (53.00 g, 0.744 mol) in benzene (100mL) was refluxed using a Dean-Stark trap. After 2 h no more water was produced. The solution was evaporated and the residue was distilled [bp 114.5-117°C (14 mm)] [lit[133] bp 64-65°C (0.5 mm)] to give the enamine **122** (98.09 g, 87%).

***N*-Cyclohexylidenecyclohexanamine 74**:[134] Cyclohexanone (21.58g, 0.22 mol) and cyclohexanamine (21.80 g, 0.22 mol) were added with stirring to benzene (50mL) contained in a 100-mL round-bottomed flask equipped with a Dean-Stark trap that carried a reflux condenser fitted with a Drierite drying tube. The mixture was refluxed for 2 h, by which time water was no longer produced. The solvent was evaporated and distillation of the residue gave the imine **74** (34.70 g, 88%) as a faintly yellowish liquid, bp 107-110°C (3 mm). The imine was used immediately.

***cis*- and *trans*-2-(3-Butenyl)cyclohexanols 73a and 73b:**

**a) 2-(3-butenyl)cyclohexanone 72**[135] *N*-Cyclohexylidene-cyclohexanamine **74** (5.37 g, 0.03 mol) in THF (2 mL + 1 mL rinse) was added to ethylmagnesium bromide (2.19 M in ether, 13.7 mL, 0.03 mol) in dry THF (30mL). The mixture was refluxed under argon for 20 h. 4-Bromo-1-butene (Aldrich, 4.05 g, 0.03 mol) was injected and refluxing was continued for a further 24 h. The mixture was cooled, stirred for 30 min with 2 N aqueous HCl (30mL) and extracted with ether (2 x 30 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Kugelrohr distillation of the residue [bp 95-120°C (0.8 mm)] [lit[135] bp 104-107°C (17 mm)] gave the ketone **72** which was used directly for the next stage. The material had IR (neat) 1710, 1642, 1000, 915 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80

MHz) δ 1.05–2.70 (m, 13H), 4.83–5.23 (m, 2H), 5.55–6.07 (m, 1H).

**b)** *cis*- **and** *trans*-**2-(3-butenyl)cyclohexanols 73a and 73b**.[136] For the preparation of alcohols **73a** and **73b** it was found advantageous to use the crude ketone **72**. The material from the above experiment was dissolved in ether (10 mL) and a solution of lithium aluminum hydride (Aldrich, 1 M in THF, 10 mL, 0.01 mol) was injected rapidly with stirring and under argon. After a further 10 min the mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ether (2 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Kugelrohr distillation of the residue [bp 125–135°C (12 mm)] gave alcohols **73a** and **73b** (3.37 g, 73% overall from **74**) in a ratio ($^1H$ NMR) of 1:4.3 as an apparently homogeneous (TLC, silica, 8:2 hexane–ethyl acetate) oil: IR (neat) 3100–3660, 1642, 1000, 914 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) δ 0.75–2.50 (m, 14H), 3.17 (*trans*–isomer, broad dt, J = 8.0, 4.0 Hz, 0.81 H), 3.85 (*cis*–isomer, broad m, $J_{1/2}$ = 10.0 Hz, 0.19 H), 4.80–5.20 (m, 2H), 5.55–6.10 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) δ *cis*–isomer **73a** 20.6, 25.2, 26.6, 31.2, 31.3, 33.1, 40.7, 69.4, 114.5, 139.3; *trans*–isomer **73b** 25.0, 25.6, 30.1, 31.0, 31.6, 35.8, 44.7, 74.7, 114.4, 139.5.

*cis*- **and** *trans*-**1*H*-Imidazole-1-carbothioic acid *O*-[2-(3-butenyl)cyclohexyl] esters 75a and 75b**. *cis*- and *trans*-Alcohols **73a** and **73b** (0.542 g, 3.51 mmol) and 1,1'-thiocarbonylbisimidazole[137] (1.25 g, 7 mmol) were placed in a flask and covered with dry 1,2-dichloroethane (10 mL). The resulting solution was refluxed under argon for 20 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 8:2 hexane–ethyl acetate gave a 1:4.7 ($^1H$ NMR) mixture of *cis*- and *trans*-alkoxythiocarbonylimidazoles **75a** and **75b** (0.743 g, 80%) which was pure by TLC (silica, 7:3 hexane–ethyl acetate, 2 spots): IR (neat) 1639, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) δ 1.04–2.36 (m, 13H), 4.90–5.10 (m, 2H), 5.29 (*trans*–isomer, dt, J = 9.5, 4.5 Hz, 0.82 H), 5.64–5.90 (m, 1.18H), 7.04 (broad m, 1H), 7.63 (t, J = 1.2 Hz, 1H), 8.33 (t, J = 1.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) δ *cis*- isomer **75a** 21.2, 23.5, 24.9, 28.1, 29.0, 39.7, 82.8; *trans*–isomer **75b** 24.2, 24.6, 29.8, 30.3, 30.6, 31.2, 41.0, 86.9, 115.0, 117.8, 130.8, 136.7, 138.2, 183.8; exact mass, m/e 264.1298 (calcd for $C_{14}H_{20}N_2OS$, m/e 264.1296).

**Cyclization of alkoxythiocarbonylimidazoles 75a and 75b. Octahydro-1-methyl-1*H*-indenes 76a and 76b:**[111] The general procedure was followed using a mixture of *cis*- and *trans*-alkoxythiocarbonylimidazoles **75a** and **75b** (0.125 g, 0.473 mmol) in benzene (40 mL), triphenyltin hydride (0.20 mL, 0.8 mmol) in benzene (10 mL), and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent, Kugelrohr distillation (bp 145–180°C) gave a mixture of hydrocarbons (0.044 g, 68%) consisting (VPC) of *cis*-octahydro-1-methyl-1*H*-indenes **76a** and **76b** (98%) in a 1:2 ratio (VPC) of *exo* and *endo* isomers and *trans*-decahydronaphthalene **77b** (2%). The mixture of hydrocarbons had *cis*-octahydro-1*H*-indenes **76a** and **76b**: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.90 (major isomer, d, $J$ = 7.2 Hz, 2H), 0.95 (minor isomer, d, $J$ = 6.6 Hz, 1H), 1.06–2.16 [m, 16H, including 1.10 (dt, $J$ = 13.2, 3.5Hz)]; $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ major isomer 15.4, 21.1, 22.2, 25.6, 26.2, 27.4, 30.6, 38.7, 39.7, 43.7, minor isomer 20.3, 22.4, 24.8, 27.2, 27.8, 29.0, 29.8, 32.0, 39.3, 47.1; exact mass, m/e 138.1390 (calcd for $C_{10}H_{18}$, m/e 138.1408). Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.12; H, 12.85. *trans*-decahydronaphthalene **77b**: $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ 26.8, 34.3, 43.7; authentic (Aldrich) *trans*-decahydronaphthalene **77b**: $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 26.8, 34.3, 43.6; authentic (Aldrich) *cis*-decahydronaphthalene **77a**: $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 24.2 (broad s), 29.4 (broad s), 36.5.

**1-Tridecen-6-ol 79:** 1-Octanal (0.49 g, 3.85 mmol) in THF (2 mL + 1 mL rinse) was added dropwise to the Grignard reagent formed from magnesium turnings (0.097 g, 4 mmol) and 5-bromo-1-pentene[139] (0.60 g, 4.0 mmol) in dry THF (30 mL). After 1 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 9:1 hexane–ethyl acetate gave alcohol **79** (0.41 g, 54%) as a pure (TLC, silica, 8:2 hexane–ethyl acetate) oil which had: IR (neat) 3120–3660, 1647, 919 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 0.87 (t, $J$ = 6.4 Hz, 3H), 1.02–1.75 (m, 17H), 1.85–2.40 (m, 2H), 3.43–3.81 (broad m, 1H), 4.85–5.20 (m, 2H), 5.55–6.13 (m, 1H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 14.1, 22.7, 25.0, 25.7, 29.3, 29.7, 31.9, 33.8, 37.0, 37.6, 71.9, 114.6, 138.8.

**1*H*-Imidazole-1-carbothioic acid *O*-(1-tridecene-6-yl) ester 80**: Alcohol **79** (0.37 g, 1.87 mmol) and 1,1'-thiocarbonylbisimidazole[111] (0.45 g, 2.5 mmol) were placed in a flask and covered with dry 1,2-dichloroethane (10 mL). The resulting solution was refluxed under argon for 19 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 8:2 hexane–ethyl acetate gave pure (TLC, silica, 7:3 hexane–ethyl acetate) **80** (0.42 g, 73%): IR (neat) 1645, 919 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 0.87 (t, J = 6.0 Hz, 3H), 1.02–1.90 (m, 16H), 2.10 (q, J = 6.8 Hz, 2H), 4.87–5.17 (m, 2H), 5.43–6.04 (m, 2H), 7.00 (broad s, 1H), 7.58 (broad s, 1H), 8.29 (broad s, 1H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 14.0, 22.6, 24.4, 25.1, 29.1, 29.4, 31.7, 32.8, 33.4, 85.1, 115.2, 117.9, 130.7, 136.7, 137.9, 184.1; exact mass m/e 308.1923 (calcd for $C_{17}H_{28}N_2OS$, m/e 308.1922). Anal. Calcd for $C_{17}H_{28}N_2OS$: C, 66.19; H, 9.15; N, 9.08. Found: C, 67.08; H, 9.29; N, 8.78.

**Cyclization of alkoxythiocarbonylimidazole 80; *cis*- and *trans*–1–heptyl–2–methylcyclopentanes 82**: The general procedure was followed using **80** (0.146 g, 0.473 mmol) in benzene (40 mL), triphenyltin hydride (0.13 mL, 0.5 mmol) in benzene (10 mL), and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent, Kugelrohr distillation (bp 200–230°C) of the residue gave 1–heptyl–2–methyl–cyclopentane **82** (0.055 g, 63%) as a mixture of isomers in a ratio (VPC) of 1:2.5 as a pure (> 99%, VPC) oil which had: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.80 (major isomer, d, J = 7.2 Hz, 2.14H), 0.90 (t, J = 6.1 Hz, 3H), 0.97 (minor isomer, d, J = 6.6 Hz, 0.86H), 1.00–1.44 (m, 14H), 1.46–1.60 (m, 1.5H), 1.60–1.90 (m, 3H), 1.96–2.06 (m, 0.5H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ major isomer: 14.1, 14.8, 22.7, 28.9, 29.4, 29.8, 30.1, 30.6, 32.0, 33.6, 34.9, 36.0, 43.4; minor isomer: 19.5, 22.6, 23.6, 28.6, 32.5, 40.7, 47.8; exact mass m/e 182.2033 (calcd for $C_{13}H_{26}$, m/e 182.2034).

**1-(3-Butenyl)-2-oxocyclopentanecarbocyclic acid ethyl ester 86**:[116] Sodium hydride (33% oil dispersion, 0.71 g, 0.0296 mol) was suspended in dry THF (20 mL) under argon and 2-oxocyclopentanecarboxylic acid ethyl ester (Aldrich, 4.30 mL, 0.029 mol) was added dropwise with stirring. The resulting slurry was refluxed for 2 h and then cooled to room temperature. 4-Bromo-1-butene (Aldrich, 3.25 mL, 0.032 mol) was injected and stirring was continued for 20 h. The mixture was then refluxed for 6 h. The solvent was evaporated and the residue was poured into water (30 mL) and extracted with ether (3 x 20 mL). The combined ether extracts were washed with saturated aqueous sodium chloride (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 mL) with 8:2 hexane–ethyl acetate) gave pure (TLC, silica, 8:2 hexane–ethyl acetate) **86** (1.83 g, 30%): IR (neat) 1750, 1720, 1644, 920 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 1.23 (t, J = 7.6 Hz, 3H), 1.50–2.50 (m, 8H), 2.50 (q, J = 7.0 Hz, 2H), 4.14 (q, J = 7.4 Hz, 2H), 4.75–5.15 (m, 2H), 5.45–6.08 (m, 1H).

**1-(3-Butenyl)-2-hydroxycyclopentanecarboxylic acid ethyl esters 87**: A solution of sodium borohydride (0.09 g, 2.47 mmol) in water (5 mL) was added dropwise with stirring to ketoester **86** (0.52 g, 2.47 mmol) in 95% ethanol (10 mL). Five minutes after the end of the addition, saturated aqueous sodium chloride (5 mL) was aded and the mixture was extracted with ether (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 8:2 hexane–ethyl acetate gave an apparently homogeneous (TLC, silica, 7:3 hexane–ethyl acetate) oil consisting (NMR) of a mixture of alcohols **87** (0.43 g, 82%) in a ratio ($^1$H NMR) of 1.1:1. The material had IR (neat) 3160–3660, 1725, 1643, 918 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 1.23 (t, J = 8.3 Hz, 1.5H), 1.25 (t, J = 8.0Hz, 1.5H), 1.43–2.75 (m, 11H), 3.00 (broad m, 0.5H), 4.00 (m, 0.5H), 4.13 (q, J = 7.0 Hz, 1H), 4.15 (q, J = 7.2Hz, 1H), 4.75–5.20 (m, 2H), 5.47–6.05 (m, 1H); $^{13}$C NMR ($CDCl_3$, 22.6 MHz) $\delta$ 14.3, 19.8, 20.4, 29.6, 29.7, 31.1, 31.5, 32.0, 32.3, 35.7, 57.3, 58.1, 60.5, 60.6, 79.3, 114.7, 114.8, 138.1, 138.4, 176.3, 176.5; exact mass, m/e 212.1411 (calcd for $C_{12}H_{20}O_3$, m/e 212.1412).

**1*H*–Imidazole–1–carbothioic acid *O*–[2–(3–butenyl)–2–carbethoxy–cyclopentyl]ester 88**: Alcohols **87** (0.34 g, 1.60 mmol) and 1,1'-thiocarbonylbisimidazole[117] (0.57 g, 3.2 mmol) were placed in a flask and covered with dry 1,2-dichloroethane (10 mL). The resulting solution was refluxed under argon for 20 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 7:3 hexane–ethyl acetate gave a pure (TLC, silica, 7:4 hexane–ethyl acetate, 2 spots) oil consisting ($^1$H NMR) of the alkoxythiocarbonylimidazoles **88** (0.44 g, 85%) in a ratio ($^1$H NMR) of 1.1:1. The

material had IR (neat) 1730, 1644, 919 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.15 (minor isomer, t, J = 8.1 Hz, 1.4H), 1.30 (major isomer, t, J = 7.5 Hz, 1.6H), 1.66–2.20 (m, 8H), 2.20–2.30 (m, 1H), 2.40–2.50 (m, 1H), 4.12 (minor isomer, dq, J = 8.0, 2.0 Hz, 0.9H), 4.24 (major isomer, q, J = 8.0 Hz, 1.1H), 4.10–4.30 (m, 2H), 5.72 (minor isomer, dd, J = 5.3, 2.8 Hz, 0.45H), 5.70–5.86 (m, 1H), 6.14 (major isomer, dd, J = 5.5, 3.1 Hz, 0.55H), 7.05 (minor isomer, broad s, 0.45H), 7.08 (major isomer, broad s, 0.55H), 7.55 (minor isomer, broad s, 0.45H), 7.63 (major isomer, broad s, 0.55H), 8.29 (minor isomer, broad s, 0.45H), 8.35 (major isomer, broad s, 0.55H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) δ 14.2, 21.0, 29.0, 30.0, 30.2, 30.4, 31.3, 32.7, 39.2, 58.5, 60.9, 61.2, 88.1, 91.7, 115.3, 177.7, 118.1, 130.9, 136.3, 136.7, 137.2, 137.4, 172.8, 174.1; exact mass m/e 322.1352 (calcd for $C_{16}H_{22}N_2O_3S$ m/e 322.1351). Anal. Calcd for $C_{16}H_{22}N_2O_3S$: C, 59.60; H, 6.88; N, 8.69. Found: C, 59.87; H, 6.91; N, 8.75.

**Cyclization of alkoxythiocarbonylimidazoles 88; (1α, 3aα, 6aα)- and (1α, 3aβ, 6aβ)-hexahydro-1-methyl-3a-(1*H*)-pentalenecarboxylic acid ethyl esters 90:** The general procedure was followed using a mixture of alkoxythiocarbonylimidazoles **88** (0.135 g, 0.42 mmol) in benzene (40 mL), triphenyltin hydride (0.13 mL, 0.5mmol) in benzene (10 mL) and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent, Kugelrohr distillation [bp 130–140°C (90 mm)] gave **90** (0.053 g, 64%) as an apparently homogeneous (TLC, silica, 9:1 hexane–ethyl acetate) oil consisting ($^1$H NMR) of a 1.6:1 mixture of isomers. The material had IR (neat) 1725 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.98 (major isomer, d, J = 6.8Hz, 2.6H), 1.02 (minor isomer, d, J = 6.8Hz, 0.4H), 1.26 (t, J = 8.3 Hz, 3H), 1.20–1.38 (m, 2H), 1.40–1.78 (m, 6H), 2.04 (major isomer, dt, J = 12, 6.8 Hz, 1.7H), 2.12 (minor isomer, dt, J = 12, 6.8 Hz, 0.3H), 2.20 (minor isomer, m, 0.14H), 2.37 (m, 1H), 2.60 (major isomer, q, J = 8.3 Hz, 0.86 H), 4.15 (q, J = 8.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) δ major isomer: 14.2, 14.9, 27.3, 28.0, 32.6, 37.3, 37.6, 39.4, 53.5, 60.2, 179.0, minor isomer: 19.4, 25.8, 31.2, 32.2, 35.3, 38.4, 38.5, 42.4, 59.9; exact mass m/e 196.1466 (calcd for $C_{12}H_{20}O_2$ m/e 196.1463).

**1-(3-Butenyl)-2-chlorocyclohexanol 92:** 3-Butenylmagnesium bromide was prepared in dry ether (30 mL) from magnesium turnings (0.24 g, 10 mmol) and

4-bromo-1-butene (Aldrich, 1.0 mL, 10 mmol) and used as follows, acording to a general procedure[134] The reagent was cooled to −60°C and 2-chlorocyclohexanone[140] (1.19 g, 0.009 mol) in ether (10 mL) was added dropwise. The mixture was stirred for 30 min at −60°C, cooled to −70°C and then acetic acid (0.1 mL, 1.6 mmol) was added.[141] The solution was allowed to warm to room temperature over *ca.* 30 min (by removal of the cooling bath). Water (10 mL) was added and the aqueous phase was separated and extracted with ether (2 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Thin layer chromatography of the crude product showed two major spots. That of higher Rf **92** (0.510 g, 30%) was isolated by flash chromatography over silica gel (2 x 15 cm) with 8:2 hexane–ethyl acetate. The material was obtained as a homogeneous (TLC, silica, 8:2 hexane–ethyl acetate) oil: IR (neat) 3565, 3100–3640, 1642, 914 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.23–2.24 [m, 13H, including 1.50 (ddt, $J$ = 13.5, 4.0, 1.0 Hz), 1.89 (d, $J$ = 2.0 Hz), 2.05 (ddq, $J$ = 14.0, 4.5, 2.0 Hz)], 4.01 (dd, $J$ = 10.5, 4.8 Hz, 1H), 4.99 (qd, $J$ = 10.2, 2.0 Hz, 1H), 5.07 (qd, $J$ = 16.9, 2.0 Hz, 1H), 5.86 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) $\delta$ 20.9, 25.4, 27.7, 32.6, 34.6, 39.8, 69.2, 72.8, 114.7, 138.6; exact mass, $m/e$ 188.0964 (calcd for $C_{10}H_{17}ClO$, $m/e$ 188.0968).

**Cyclization of chlorohydrin 92: (1$\alpha$, 3a$\beta$, 7a$\beta$)- and (1$\alpha$, 3a$\alpha$, 7a$\alpha$)-octahydro-1-methyl-3a*H*-inden-3a-ols 94**: The general procedure was followed using chlorohydrin **92** (0.043 g, 0.226 mmol) in benzene (40 mL), triphenyltin hydride (0.06 mL, 0.25 mmol) in benzene (10 mL), and AIBN (0.007 g, 0.05 mmol) in benzene (10 mL). After evaporation of the solvent, flash chromatography of the residue over silica gel (1 x 15 cm) with 8:2 hexane–ethyl acetate gave *cis*-fused alcohols **94** (0.017 g, 49%) as a 1:2 mixture ($^1H$ NMR) of isomers. The material was apparently homogeneous (TLC, silica, 7:3 hexane–ethyl acetate) and had: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.82 (dq, $J$ = 13.3, 3.2 Hz, 0.25H), 0.92 (major isomer, d, $J$ = 7.2 Hz, 2H), 1.00 (minor isomer, d, $J$ = 7.1 Hz, 1H), 1.05–2.05 (m, 11.7 Hz, 3H), 2.62 (m, $J$ = 7.2 Hz, 0.53H); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ major isomer: 15.1, 24.2, 24.4, 25.1, 29.4, 34.4, 35.0, 36.7, 51.5; minor isomer: 21.0, 21.4, 22.2, 24.3, 29.7, 30.4, 34.6, 35.1, 39.1, 53.0; exact mass, $m/e$ 139.1125 [calcd for $C_9H_{15}O$ ($M^+ - CH_3$), $m/e$ 139.1123].

**6-Bromo-3-methyl-1-phenylhex-1-yn-3-ol 101**: Ethylmagnesium bromide (2.19 M in ether, 4.6 mL, 10 mmol) was added dropwise with stirring to phenylacetylene (Aldrich, 1.02 g, 10 mmol) in ether (20 mL). The mixture was stirred for 20 h at room temperature and 5-bromo-2-pentanone[14] (1.65 g, 10 mmol) was then added. After a further period of 15 min, water (20 mL) was added and the mixture was extracted with ether (2 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm) with 8:2 hexane–ethyl acetate gave crude **101** (2.48 g, 93%): IR (neat) 3140–3660, 1603 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 1.58 (s, 3H), 1.75–2.40 (m, 4H), 2.33 (s, 1H), 3.48 (t, J = 6.0 Hz, 2H), 7.27 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) $\delta$ 28.4, 30.3, 33.8, 42.2, 68.1, 83.9, 92.4, 122.6, 128.4, 128.5, 131.8; exact mass m/e 268.0278 (calcd for $C_{13}H_{15}BrO$ m/e 268.0286). The material contained trace impurities ($^{13}C$ NMR) but was used directly for the next stage.

**Cyclization of 101: (*Z*)- and (*E*)-2-benzylidene-1-methylcyclopentanols 103a and 103b**: The general procedure was followed using **101** (0.375 g, 1.40 mmol) in benzene (40 mL), tri-*n*-butyltin hydride (0.47 mL, 1.8 mmol) in benzene (10 mL), and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent, flash chromatography of the residue over silica gel (1.5 x 15 cm) with 8:2 hexane–ethyl acetate gave a mixture of (*Z*)- and (*E*)-alkenols **103a** and **103b** (0.173 g, 65%). The isomers were separated by flash chromatography over silica gel (1.5 x 5 cm) with 8:2 hexane–ethyl acetate to afford pure (TLC, silica, 8:2 hexane–ethyl acetate) (*Z*)-2-benzylidene-1-methyl-cyclopentanol **103a** (0.059 g, 22%, Rf = 0.39): IR (neat) 3140–3640, 1604 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.37 (s, 3H), 1.65 (m, 1H), 1.70–1.95 (m, 2H), 1.90 (s, 1H), 2.60 (m, 2H), 6.50 (broad t, J = 2.0 Hz, 1H), 7.25 (m, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 22.0, 26.5, 35.3, 45.3, 78.5, 124.1, 126.5, 128.0, 129.3, 137.3, 149.5; exact mass m/e 188.1200 (calcd for $C_{13}H_{16}O$ m/e 188.1201). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 80.88; H, 8.49, and (*E*)-2-benzylidene-1-methyl-cyclopentanol **103b** (0.114 g, 43.1%, Rf = 0.13): IR (neat) 3130–3680, 1601 cm$^{-1}$; $^1H$NMR ($CDCl_3$, 400 MHz) $\delta$ 1.46 (s, 3H), 1.66–1.94 (m, 4H), 1.83 (s, 1H), 2.71 (m, 2H), 6.54 (t, J = 2.7 Hz, 1H), 7.23 (m, 1H), 7.36 (m, 4H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 22.2, 27.2, 30.2, 41.5, 80.1, 121.3, 126.4, 128.2, 128.5, 137.9, 151.0; exact mass m/e 188.1198 (calcd for $C_{13}H_{16}O$ m/e

188, 120).

**2-(4-Bromobutoxy)tetrahydro-2*H*-pyran 182**:[143] 4-Bromo-1-butanol[144] (39.35 g, 0.257 mol) was added rapidly with stirring to dihydropyran (21.87 g, 0.26 mol) contained in a 100-mL round-bottomed flask which was equipped with a reflux condenser closed by a Drierite drying tube. After the initial exothermic reaction had subsided (*ca.* 30 min) the mixture was distilled [bp 102-107°C (12 mm)] to give the protected alcohol **182** (41.87 g, 69%).

**5-Undecyn-1-ol 105**:[145] 1-Heptyne[146] (0.96 g, 0.01 mol) in dry THF (25 mL) was placed in a 10-mL round-bottomed flask under argon and the solution was cooled to −70°C in a dry ice–acetone bath. *n*–Butyllithium (1.2 M in hexane, 9.1 mL, 0.011 mole) was added dropwise via syringe (over *ca.* 5 min) and the mixture was stirred for 15 min after the end of the addition. HMPA (1.75 mL, 0.01 mol) was then added and 2–(4–bromobutoxy)tetrahydro–2*H*–pyran **182** (2.61 g, 0.011 mol) in THF (2 mL + 1 mL rinse) was injected (over *ca.* 1 min) into the acetylide solution. The cooling bath was removed and the mixture was allowed to warm to room temperature. After 48 h, the solvent was evaporated and the residue was dissolved in ether (35 mL). The protecting group was removed by stirring the ether solution for 2 h with 3 N aqueous HCl (10 mL). The aqueous layer was separated and extracted with ether (2 x 20 mL). The combined extracts were washed with saturated cupric sulfate solution (to remove HMPA), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 8:2 hexane–ethyl acetate gave **105** (0.51 g, 30%) as a homogeneous (TLC, silica, 8:2 hexane–ethyl acetate) oil: IR (neat) 3030–3640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.89 (t, $J$ = 7.0 Hz, 3H), 1.10–1.80 (m, 6H), 2.00–2.60 (m, 5H), 3.65 (broad t, $J$ = 6.4 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 14.0, 18.7, 22.2, 23.2, 28.7, 31.1, 61.4, 76.2, 82.7.

**1-Phenyl-7-tridecyne-3-ol 106**:

**a) 1-Oxo-5-undecyne 183**: 5-Undecyne-1-ol (0.38 g, 2.26 mmol) in dichloromethane (2 mL + 1 mL rinse) was added to a stirred mixture of pyridinium chlorochromate (1.72 g, 8 mmol) and 3A Molecular sieves (*ca.* 2 g) in dichloromethane

(25 mL). The mixture was stirred for 1 h at room temperature and the resulting brown slurry was filtered by suction through a pad of "normal" silica gel (2 × 4 cm) using hexane for washings. Removal of the solvents gave the crude aldehyde (IR) which was used directly for the next stage.

**b) 1-Phenyl-7-tridecyne-3-ol 106**. The Grignard reagent prepared in ether (5 mL) from magnesium turnings (0.097 g, 4 mmol) and (2-chloroethyl)benzene (0.4218 g, 3 mmol) was added dropwise (*ca.* 1 min) to a stirred solution of the above aldehyde in ether (20 mL). After a further period of 15 min, the stirred reaction mixture was quenched by dropwise addition of saturated aqueous ammonium chloride (2 mL). The organic phase was separated, the aqueous layer was extracted with ether (1 × 10 mL) and the combined organic solution was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 × 5 cm) with 8:2 hexane–ethyl acetate gave the pure (TLC, silica, 8:2 hexane–ethyl acetate) alcohol **106** (0.40 g, 66%); IR (neat) 3120–3670, 1607 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.89 (t, $J$ = 6.0 Hz, 3H), 1.10–2.40 (m, 17H), 2.75 (dt, $J$ = 7.4, 3.6 Hz, 2H), 3.66 (broad m, 1H), 7.06–7.40 (broad s, 5H); $^{13}C$ NMR ($CDCl_3$, 15.08 MHz) $\delta$ 14.0, 18.8, 22.3, 25.3, 28.9, 31.2, 32.1, 36.8, 39.2, 71.0, 79.8, 80.9, 125.9, 128.5, 142.5; exact mass, $m/e$ 272.2134 (calcd for $C_{19}H_{28}O$, $m/e$ 272.2140).

**1*H*-Imidazole-1-carbothioic acid *O*-(1-phenyl-7-tridecyn-3-yl) ester 107**. Alcohol **106** (0.36 g, 1.32 mmol) and 1,1'-thiocarbonylbisimidazole[illegible] (0.45 g, 2.50 mmol) were placed in a flask and covered with dry 1,2-dichloroethane (10 mL). The resulting solution was refluxed under argon for 36 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) using 7:3 hexane–ethyl acetate gave the pure (TLC, silica, 7:3 hexane–ethyl acetate) alkoxythiocarbonylazole **107** (0.330 g, 65%) as an oil; IR (neat) 1609 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.89 (t, $J$ = 6.0 Hz, 3H), 1.10–2.35 (m, 16H), 2.75 (dt, $J$ = 8.4, 3.0 Hz, 2H), 5.68 (q, $J$ = 6.0 Hz, 1H), 7.00 (broad s, 1H), 7.05–7.40 (broad s, 5H), 7.55 (broad s, 1H), 8.2 (broad s, 1H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 13.9, 18.6, 22.2, 24.5, 28.8, 31.1, 31.6, 32.3, 34.9, 78.9, 84.1, 117.9, 126.2, 128.2, 128.5, 130.7, 136.7, 183.9; exact mass, $m/e$ 382.2081 (calcd for $C_{23}H_{30}N_2OS$, $m/e$ 382.2079). Anal. Calcd for $C_{23}H_{30}N_2OS$: C, 72.21; H, 7.90; N, 7.32. Found: C, 72.25; H, 7.90; N, 7.07.

**Cyclization of alkoxythiocarbonylimidazole 107; (*E*)-1-hexylidene-2-(2-phenylethyl)cyclopentane 109**: The general procedure was followed using the alkoxythiocarbonylimidazole **107** (0.175 g, 0.458 mmol) in benzene (40 mL), triphenyltin hydride (0.16 mL, 0.6 mmol) in benzene (10 mL), and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent, flash chromatography of the residue over silica gel (1.5 x 15 cm) with hexane gave the alkene **109** (0.095 g, 81%) as a pure (TLC, silica, hexane) oil: IR (neat) 1606 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.89 (t, J = 7.0 Hz, 3H), 1.20–1.44 (m, 7H), 1.48–1.64 (m, 2H), 1.80 (m, 1H), 1.89–2.08 (m, 4H), 2.16–2.40 (m, 3H), 2.56–2.80 (m, 2H), 5.23 (qt, J = 7.2, 2.4 Hz, 1H), 7.16–7.39 (m, 5H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 14.1, 22.7, 24.2, 29.2, 29.4, 31.7, 32.8, 34.2, 36.6, 43.9, 120.4, 125.6, 128.3, 128.4, 143.1, 146.1; exact mass, m/e 256.2190 (calcd for $C_{19}H_{28}$, m/e 256.2191). Anal. Calcd for $C_{19}H_{28}$: C, 88.99; H, 11.01. Found: C, 88.80; H, 11.07.

**Ozonolysis of Compound 109**: This experiment was done by Lu Set. Ozone was bubbled for 20 min through a solution of alkene **109** (0.047 g, 0.18 mmol) in methanol (6 mL) at −78°C. Excess of ozone was removed by a stream of argon (ca. 5 min) and dimethylsulfide (5 drops) was added to the mixture which was then stirred for 2 h and allowed to warm to room temperature. The solvent was evaporated and flash chromatography of the residue over silica gel (1 x 20 cm) with 95:5 hexane–ethyl acetate gave cyclopentanone **110** as a pure (TLC, silica, 9:1 hexane–ethyl acetate) oil which had: IR (neat) 1740 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.60 (m, 2H), 1.80 (m, 1H), 2.00–2.24 (m, 4H), 2.24–2.38 (m, 2H), 2.62–2.81 (m, 2H), 7.15–7.38 (m, 5H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 20.6, 29.6, 31.3, 33.5, 38.0, 48.2, 125.8, 128.2, 141.5, 220.9. The materia[illegible] was compared spectroscopically with an authentic sample (see p. 183).

**Keto ester 111**:[46] This experiment was done by Lu Set. (2-Bromoethyl)benzene[48] (1.45 mL, 1.062 mmol) in DMSO (1 mL + 1 mL rinse) was added dropwise (ca. 2 min) to a solution of the potassium salt of 2-oxocyclopentanecarboxylic acid ethyl ester[49] (2.065 g, 1.062 mmol) in dry DMSO (10 mL) under nitrogen. The mixture was stirred overnight at room temperature, poured into water (30 mL) and extracted w[illegible]entane (3 x 15 mL). The combined extracts were dried (MgSO$_4$) and evaporated. The crude material was used directly in the next step.

**Authentic 2-(2-phenylethyl)cyclopentanone 110:**[147] This experiment was done by Lu Set. Crude ketoester **111** was refluxed overnight in 3 N HCl (100 mL). After being cooled to room temperature, the solution was extracted with pentane (3 x 20 mL). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (20 mL) and saturated aqueous sodium chloride (20 mL). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm) with 8:2 hexane–ethyl acetate gave pure (TLC, silica, 8:2 hexane–ethyl acetate) 2-(2-phenylethyl)cyclopentanone **110** (0.721 g, 36%). The material was identical (TLC, IR, $^1$H NMR, $^{13}$C NMR) with the ketone **110** obtained by ozonolysis of alkene **109**. It had: IR (neat) 1735 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.53 (m, 2H), 1.70 (m, 1H), 1.89–2.15 (m, 4H), 2.15–2.34 (m, 2H), 2.56–2.77 (m, 2H), 7.10–7.30 (m, 5H); $^{13}$C NMR ($CDCl_3$, 22.6 MHz) $\delta$ 20.7, 29.7, 31.4, 33.6, 38.2, 48.4, 125.9, 128.4, 141.6, 220.9; exact mass, m/e 188.1202 (calcd for $C_{13}H_{16}O$, m/e 188.1201).

**(4-Bromo-1-butynyl)benzene 114:**[150] Bromine (1.60 g, 0.01 mol) was added dropwise to a stirred solution of triphenyl phosphite (3.10 g, 0.01 mol) in dry ether (50 mL) at 0°C. 4-Phenyl-3-butyn-1-ol[151] (1.46 g, 0.01 mol) and pyridine (0.9 mL, 0.01 mol) in ether (10 mL) were added dropwise and the resulting white slurry was stirred for 48 h at room temperature. Water (50 mL) was added and the mixture was extracted with ether (2 x 50 mL). The combined extracts were washed with 3 N aqueous HCl (30 mL), dried ($MgSO_4$) and evaporated. Chromatography of the residue over "normal" silica gel (2.5 x 15 cm) with 9:1 hexane–ethyl acetate and Kugelrohr distillation [bp 135–140°C (9 mm)] gave the pure (TLC, silica, 9:1 hexane–ethyl acetate) bromide (1.55 g, 74%): IR (neat) 1596 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 2.90 (t, J = 7.2 Hz, 2H), 3.48 (t, J = 6.8 Hz, 2H), 7.30 (m, 5H); $^{13}$C NMR ($CDCl_3$, 15.1 MHz) $\delta$ 23.9, 29.5, 82.5, 86.6, 123.3, 128.1, 128.3, 131.8.

**4-Phenyl-3-butyn-1-ol 4-methylbenzenesulfonate 115:** 4–Phenyl–3–butyne–1–ol[151] (2.11 g, 14.43 mmol), pyridine (3.5 mL, 43 mmol), *p*–toluenesulfonyl choride (3.05 g, 16 mmol) and a catalytic amount of *N,N*–dimethyl–4–aminopyridine (0.010 g, 0.08

mmol) were added in that order to dry benzene (50 mL) and the solution was stirred at room temperature for 4 days. The mixture was poured into water (50 mL) and the organic phase was washed with 3 *N* aqueous HCl (2 x 20 mL). It was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 8:2 hexane–ethyl acetate gave pure (TLC, silica, 7:3 hexane–ethyl acetate) tosylate **115** (2.26 g, 52%): IR (neat) 1601, 1360, 1175 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 2.40 (s, 3H), 2.75 (t, J = 7.0 Hz, 2H), 4.18 (t, J = 7.0 Hz, 2H), 7.25 (m, 7H), 7.79 (d, J = 8.4 Hz, 2H).

**4-Bromo-1-butyne 113:**[152] Bromine (15.98 g, 5.12 mL, 0.1 mol) was added dropwise to a solution of triphenyl phosphite (34.13 g, 0.11 mol) in dry ether (50 mL) at 0°C. 3-Butyne-1-ol (Aldrich, 7.01 g, 0.1 mol) and pyridine (8.9 mL, 0.11 mol) in dry ether (25mL) were added dropwise and the resulting white slurry was stirred for 20 h at room temperature. The mixture was poured into water (50 mL) and extracted with ether (2 x 50mL). The combined extracts were washed with 3 *N* aqueous HCl (20 mL), dried ($MgSO_4$) and evaporated. Distillation (bp 95–96°C) gave bromide **113** (4.07 g, 30%): IR (neat) 3295, 2125 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 2.10 (t, J = 2.0 Hz, 1H), 2.72 (dt, J = 8.5, 2.0 Hz, 2H), 3.43 (t, J = 7.0 Hz, 2H).

**3-Nonyn-1-ol 184:**[153] Ethylmagnesium bromide was prepared from magnesium turnings (25 g, 1.03 mol) and bromoethane (109.0 g, 75 mL, 1.0 mol) in dry ether (1000 mL). 1-Heptyne[146] (96.17 g, 1 mol) was added dropwise (over *ca.* 1 h) and the solution was refluxed for 20 h. It was cooled to 0°C, the flask was equipped with a dry ice reflux condenser, and ethylene oxide (Eastman, 100 g, 2.27 mol) in ether (50 mL) was added dropwise (over *ca.* 30 min). Stirring was continued for a further 2 h at which stage the mixture solidified. Aqueous 6 *N* HCl was added slowly at 0°C and the solids dissolved. The mixture was extracted with ether (3 x 100mL) and the combined extracts were washed with saturated aqueous sodium chloride (100 mL), dried ($Na_2SO_4$) and evaporated. Distillation [bp 104–105°C (9 mm)] gave the pure (TLC, silica, 8:2 hexane–ethyl acetate) alcohol **184** (71.0 g, 50%): IR (neat) 3060–3640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.90 (t, J = 7.9 Hz, 3H), 1.10–1.90 (m, 11H), 2.15 (m, 4H), 3.63 (t, J = 5.0 Hz, 2H).

**1-Bromo-3-nonyne 117:**[134] Bromine (11.60 mL, 0.226 mol) was added dropwise to a stirred solution of triphenyl phosphite (70.25 g, 0.226 mol) in ether (200mL) at 0°C. Alcohol **184** (28.04 g, 0.2mol) and pyridine (18.3 mL, 0.226 mol) in ether (25 mL) were added slowly (over *ca.* 30 min) and the resulting white slurry was stirred for 24 h at room temperature. The reaction mixture was poured into water (50 mL) and extracted with ether (2 x 50 mL). The combined extracts were washed with 3 N aqueous HCl (30 mL), dried ($MgSO_4$) and evaporated. The residue was distilled [bp 107−108°C (14 mm)] to give the bromide (35.45 g, 87%) which was pure (> 98% VPC) and had IR (neat) no OH band; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.90 (t, J = 6.6 Hz, 3H), 1.00−1.70 (m, 6H), 2.13 (m, 2H), 2.70 (tt, J = 7.6, 2.5 Hz, H), 3.41 (t, J = 7.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) $\delta$ 14.0, 18.7, 22.2, 23.4, 28.6, 30.4, 31.1, 82.8.

**Alkyla[illegible]n of *N*-cyclohexylidene-cyclohexanamine 74 with 1−bromo−3−nonyne 117; 2−(3−nonynyl)cyclohexanone 118:** Lithium diisopropylamide (LDA) was prepared at −20°C by addition of *n*−butyllithium (1.6 M in hexane, 6.8 mL, 11mmol) to a solution of diisopropylamine (1.11 g, 11 mmol) in dry THF (20 mL). The solution was allowed to warm to 0°C over 15 min and imine **74** (p. 172, 1.79 g, 10 mmol) in THF (2 mL + 1 mL rinse) was added dropwise at this temperature. After 30 min, bromide **117** (2.03 g, 10 mmol) in THF (2 mL + 1 mL rinse) was added and the mixture was refluxed for 1 h. At this point no more bromide could be detected by VPC. The mixture was cooled to room temperature, stirred for 30 min with 3 *N* aqueous HCl (10 mL) and extracted with ether (2 x 20 mL). The combined extracts were washed with 3 *N* aqueous HCl (10 mL), dried ($MgSO_4$) and evaporated to afford a mixture of two products that could not be separated by TLC. The major product (60%, $^1H$ NMR) was shown (IR, $^1H$ NMR, $^{13}C$ NMR) to be an allene: IR (neat) 1960, 1710 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.90−2.50 (m, 22H), 4.95 (q', J = 4.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) $\delta$ 212.8. The minor isomer (40%, $^1H$ NMR) was the desired acetylenic ketone **118**: IR (neat) 1711 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.90 (t, J = 6.4Hz, 3H), 1.00−2.60 (m, 21H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) $\delta$ 14.0, 16.5, 18.8, 22.3, 25.2, 28.1, 28.8, 31.1, 33.9, 42.2, 49.4, 79.6, 80.8, 212.9.

**1,1,4-Tribromo-1-butene 121:**

**a) 3-Bromo-1-propanal 120:**[155] The compound was made by the literature procedure.[155] Hydrogen bromide was bubbled slowly for *ca.* 2 h through a solution of propenal (12.7 mL, 0.2 mol) in dichloromethane (50mL). Excess of HBr was displaced by a stream of argon and the aldehyde solution was dried ($Na_2SO_4$) and evaporated.

**b) (Dibromomethylene) triphenylphosphorane:**[119] The reagent was prepared by the literature procedure[119] from triphenylphosphine (100.00 g, 0.381 mol), carbon tetrabromide (126.26 g, 0.381 mol) and zinc dust (24.88 g, 0.381 mol) in dichloromethane (500 mL).

**c) 1,1,4-Tribromo-1-butene 121:** The bromoaldehyde [see (a) above] in dichloromethane (50 mL) was added to the Wittig reagent [see (b) above] and the mixture was stirred mechanically overnight at room temperature. It was diluted with pentane (1000 mL) and the supernatant was decanted. The black residue was extracted twice with pentane (2 x 200 mL) and the combined pentane solutions were evaporated. The product was partially purified by passage through a pad of "normal" silica gel (5 x 20 cm) using 9:1 hexane–ethyl acetate as eluant. Spinning band distillation [bp 97–99°C (12 mm)] then gave the desired material: $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 2.67 (q, J = 7.0Hz, 2H), 3.40 (t, J = 6.2 Hz, 2H), 6.44 (t, J = 7.3 Hz, 1H).

**Attempted alkylation of 1–(1–cyclohexen–1–yl)pyrrolidine 122 with 1,1,4–tribromo–1–butene 121:** The enamine **122** (p. 172, 0.50 g, 3.31 mmol) and the tribromide **121** (p. 186, 0.99 g, 3.31 mmol) in acetonitrile (15 mL) were refluxed for 16 h under argon. The mixture was then hydrolyzed by addition of water (5 mL) and a further period (30 min) of reflux. The solvents were evaporated. The residue was extracted with ether (2 x 20 mL), dried ($MgSO_4$) and concentrated. The crude product consisted ($^1$H NMR) of cyclohexanone and the starting bromide: $^1$HNMR ($CDCl_3$, 80 MHz) $\delta$ 2.67 (q, J = 7.0 Hz, 2H), 3.40 (t, J = 6.2 Hz, 2H), 6.44 (t, J = 7.3 Hz, 1H).

**(*E*)- and (*Z*)-3-Chloro-1-iodo-2-butene 123:**[156] A mixture of (*E*)- and (*Z*)-1,3-dichloro-2-butene **124**[157] (9.74 g, 77.9 mmol) and sodium iodide (14.99 g, 100 mmol) in dry acetone (50 mL) was refluxed for 20 h. The solvent was evaporated and the residue was suspended in hexane. The resulting slurry was filtered by suction and the solvent was evaporated. Distillation of the residue [bp 76–81°C (22 mm)] gave the allylic iodide (12.24 g, 72%) as a brownish liquid which was decolorized by sonication with a drop of mercury followed by filtration through Celite (0.5 x 2 cm). The iodide was stored at −10°C over a drop of mercury. It had: $^1$H NMR (CDCl$_3$, 80 MHz) δ 2.07 (s, 0.3H), 2.10 (s, 2.7H), 3.87 (d, J = 10.0 Hz, 0.2H), 3.98 (d, J = 8.0 Hz, 1.8H), 5.83 (broad t, J = 8.5 Hz, 1H).

### (*E*) and (*Z*)2-(3-Chloro-2-butenyl)-cyclohexanones 126:[117]

**a) By alkylation of N-cyclohexylidene-cyclohexanamine 74**: *n*–Butyllithium (0.85 M in hexane, 29 mL, 25 mmol) was added dropwise to imine **74** (p. 172, 4.35 g, 24.3 mmol) in ether (25 mL) at −70°C. The solution was then stirred for 2 h at −70°C. The cooling bath was removed and stirring was continued for 2 h during which time the mixture attained room temperature. The temperature was lowered to −75°C and (*E*)– and (*Z*)–1,3–dichloro–2–butenes **124**[157] (2.75 g, 22 mmol) in ether (2 mL + 1 mL rinse) was added. The solution was stirred 24 h during which period the cooling bath and the reaction mixture attained room temperature. Aqueous 3 N HCl (10 mL) was added and the reaction mixture was stirred for 2 h at room temperature. The mixture was then extracted with ether (3 x 20 mL) and the combined extracts were dried (MgSO$_4$) and evaporated. Kugelrohr distillation [bp 90–135°C (0.7mm)] gave the pure (TLC, silica, 8:2 hexane–ethyl acetate) ketone **126** (1.40 g, 34.1%).

**(b) By alkylation of 1-(1-cyclohexen-1-yl)pyrrolidine 122**: A mixture of the enamine **122** (p. 172, 0.76 g, 5 mmol) and (*E*)– and (*Z*)–3–chloro–1–iodo–2–butene **123**[156] (p. 186, 1.08 g, 5 mmol) in acetonitrile (10 mL) was refluxed for 20 h under argon. Water (5 mL) was added and the mixture was refluxed for a further 30 min. The solvent was evaporated and the residue was extracted with ether (2 x 20 mL). The combined extracts were dried (MgSO$_4$) and evaporated. Kugelrohr distillation [bp 155–170°C (18 mm)] gave pure (TLC, silica, 8:2 hexane–ethyl acetate) ketone **126** (0.550 g, 59%).

**c) By alkylation of (1-cyclohexen-1-yloxy)trimethylsilane 127**: Methyllithium (1.24 M in ether, 2.5 mL, 2 mmol) was added dropwise to silyl enol ether **127**[158] (0.34 g, 2 mmol) in ether (10 mL) at room temperature and under argon. Stirring was continued for 15 min and (*E*)– and (*Z*)–3–chloro–1–iodo–2–butenes **123**[156] (p. 186, 0.43 g, 2 mmol) in ether (2 mL + 1 mL) rinse) was added. Stirring was continued for 48 h, the slurry was then filtered by suction and the solvent was evaporated. Kugelrohr distillation of the residue [bp 130–180°C (10 mm)] gave pure (TLC, silica, 8: 2 hexane–ethyl acetate) ketone **126** (1.75 g, 47%): IR (neat) 1712 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.44 (qd, J = 11.7, 3.6 Hz, 1H), 1.70 (m, 2H), 1.89 (m, 1H), 2.00–2.60 (m, 7H), 2.10 (d, J = 1, 3 Hz, 3H), 5.53 (qt, J = 7.0, 12 Hz, 0.86H), 5.59 (qt, J = 8.4, 1.2 Hz, 0.14H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ major isomer: 25.1, 26.2, 27.9, 28.9, 33.7, 42.0, 50.2, 123.7, 131.3, 212.0; minor isomer: 25.2, 27.7, 28.7, 30.8, 31.9, 58.8, 123.6, 125.5; exact mass, m/e 186.0811 (calcd for $C_{10}H_{15}ClO$, m/e 186.0811).

***cis-* and *trans*-2-[3-Chloro-(*E*)- and (*Z*)-2-butenyl]cyclohexanols 128:** Lithium aluminum hydride (1 M in THF, 3 mL, 3 mmol) was added dropwise to a mixture of ketones **126** (1.64 g, 8.8 mmol) in ether (20 mL). After a reaction period of 15 min the mixture was quenched with saturated aqueous ammonium chloride (2 mL) and extracted with ether (10 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2.5 x 15 cm) with 8:2 hexane–ethyl acetate gave alcohols **128** (1.20 g, 72%) as a pure (TLC, silica, 7:3 hexane–ethyl acetate) oil: IR (neat) 3100–3660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.90–2.60 (m, 12H), 2.14 (broad s, 3H), 3.30 (m, 0.3H), 3.44 (m, 0.3H), 3.88 (m, 0.3H), 3.96 (m, 0.1H), 5.45–5.68 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ 19.8, 20.3, 22.6, 22.9, 24.8, 25.0, 25.1, 25.2, 25.5, 25.8, 26.0, 26.1, 26.6, 28.4, 30.0, 30.4, 31.2, 31.7, 32.1, 32.8, 34.0, 35.4, 41.2, 45.0, 55.0, 66.0, 68.9, 70.5, 74.2, 74.4, 122.2, 124.0, 124.3; exact mass, m/e 188.0953 (calcd for $C_{10}H_{17}{}^{35}ClO$, m/e 188.0968).

**Dehalogenation of alcohols 128; *cis*– and *trans*–2–(3–butynyl)cyclohexanols 119a and 119b:** The potassium salt of 1,3–diamino propane (KAPA) (6.5 mmol) was prepared by dissolving potassium hydride (24% oil dispersion, 1.05 g, 6.5 mmol) in dry 1,3–diaminopropane (5 mL) at 0°C.[111] After a reaction period of 30 min, the chloro alcohols **128** (0.1887 g, 1.0 mmol) in hexane (2 mL + 1 mL rinse) were added and the mixture was stirred for 1 h at 0°C. The reaction mixture was quenched by dropwise addition of water (3 mL), and extracted with ether (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 8:2 hexane– ethyl acetate gave pure (TLC, silica, 8:2 hexane–ethyl acetate) alcohols **119a** and **119b** (0.093 g, 60%) in a ratio ($^1$H NMR) of 1:3.8. The material had: IR (neat) 3100–3640, 3312, 2250 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 0.90–2.50 (m, 14H), 1.75 (t, J = 2.5Hz, 1H), 3.37 (*trans*–isomer, m, $J_{1/2}$ = 24 Hz, 0.80H), 4.01 (*cis*–isomer, m, $J_{1/2}$ = 8 Hz, 0.20H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ *cis*– isomer **119a**: 16.3, 23.4, 24.7, 25.1, 28.5, 29.4, 39.4, 45.5, 69.1; *trans*–isomer **119b**: 16.0, 24.9, 25.5, 30.0, 31.4, 35.9, 44.2, 68.3, 74.6; exact mass, m/e 152.1183 (calcd for $C_{10}H_{16}O$, m/e 152.1201).

**2-(2-Chloro-2-propenyl)cyclohexanone 130:**[159] Sodium amide (0.51 mol) was prepared by dissolving sodium metal (11.73 g, 0.51 mol) in liquid ammonia (200 mL) containing a few crystals of ferric nitrate. Dry benzene (200 mL) was added and the ammonia was allowed to evaporate. Cyclohexanone (49.1 g, 0.5 mol) was added and the slurry was refluxed for 18 h under argon. 2, 3–Dichloro–1–propene (55.49 g, 0.5 mol) was added and refluxing was continued for another 24 h. The mixture was cooled, poured into water (200 mL) and extracted with ether (2 x 200 mL). The combined extracts were dried (MgSO$_4$) and evaporated. Distillation [bp 111–113°C (9 mm)] gave pure (> 97%, VPC) **130** (18.00 g, 21%): IR (neat) 1710, 1635, 888 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.00–3.10 (m, 11H), 5.60 (broad s, 2H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 25.1, 28.0, 33.1, 39.1, 42.2, 47.8, 114.1, 140.8, 211.4.

**2-(2-propynyl)cyclohexanone 131 by dehalogenation of 130:**[160] Sodium amide (0.05 mol) was prepared from sodium metal (1.15 g, 0.05 mol), liquid ammonia (25 mL) and a catalytic amount of ferric nitrate. Ketone **130** (1.73 g, 0.01 mol) was added neat followed by dry benzene (50 mL). The ammonia was allowed to evaporate (stirring) and the resulting slurry was refluxed for 24 h. The reaction mixture was poured into saturated aqueous ammonium chloride (100 mL) and extracted with ether (3 x 20 mL). The combined extract was dried (MgSO$_4$) and evaporated. Kugelrohr distillation (bp 180–210°C) of the residue gave pure ($^1$H NMR) **131** (0.75 g, 55%). It was identical to material prepared by alkylation of 1–(1–cyclohexen–1–yl)pyrrolidine with 3–chloro–1–propyne (see next experiment).

**2-(2-Propynyl)cyclohexanone 131:**[160] 1-(1-Cylohexen-1-yl)pyrrolidine (p. 172) was alkylated with 3-chloro-1-propyne according to a procedure described in the literature.[160] The compound had bp 102–106°C (14 mm) [lit.[160] 93–95°C (12 mm)]; IR (neat) 3290, 2130, 1708 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.12–2.75 (m, 11H), 1.95 (t, J = 3.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 18.9, 25.1, 27.9, 33.3, 42.0, 49.6, 69.5, 82.6, 210.8.

*cis*- **and** *trans*-**2-(2-Propynyl)cyclohexanols 132a and 132b:**[160] The literature procedure[160] was followed using ketone **131** (15.50 g, 0.1138 mol) and lithium aluminum hydride (1.50 g, 0.0395 mol) in THF (50 mL). Alcohols **132a** and **132b** (13.84 g, 88%) were obtained pure (TLC, silica, 8:2 hexane–ethyl acetate) after distillation [bp 83–90 (1.4 mm)] [lit.[160] bp 81–82°C (2–3 mm)] in a ratio ($^1$H NMR) of 1:1.7 and had: IR (neat) 3060–3640, 3300, 2125 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 0.95–2.75 (m, 12H), 1.97 (t, J = 3.0Hz, 1H), 3.36 (*trans*–isomer, dt, J = 10.0, 4.5 Hz, 0.63 H), 4.04 (*cis*–isomer, broad m, 0.37H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ *cis*–isomer **132a**: 20.1, 21.5, 25.1, 26.3, 33.0, 40.9, 68.2, 69.2, 83.4; *trans-isomer* **132b**: 21.8, 24.9, 25.4, 30.3, 35.5, 43.9, 69.7, 73.4, 82.9; exact mass, m/e 138.1028 (calcd for $C_9H_{14}O$, m/e 138.1045).

*cis*- **and** *trans*-**2-(2-Butynyl)cyclohexanols 133a and 133b:** n–Butyllithium (1.29 M in hexane, 1.3 mL, 1.0 mmol) was added dropwise to a solution of alcohols **137ab** (0.065 g, 0.468 mmol) in THF (5 mL) at 0°C. The solution was stirred for 5 min and iodomethane (0.03 mL, 0.5 mmol) was added. Stirring was continued overnight at room temperature and the solution was evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm) with 7:3 hexane–ethyl acetate gave an apparently homogeneous (TLC, silica, 7:4 hexane–ethyl acetate) mixture of *cis*– and *trans*– **133ab** (0.061 g, 85%) in a ratio ($^1$H NMR) of 1:2.6 as a colorless oil: IR (neat) 3040–3640 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.07–2.04 (m, 8H), 2.00 (t, J = 2.8 Hz, 3H), 2.04–2.56 [ m, 3H, including: 2.20 (*cis*–isomer, dd, J = 6.6, 2.8 Hz), 2.25 (*cis*–isomer, dd, J = 2.9, 1.7 Hz), 2.28 (*cis*–isomer, t, J = 2.4 Hz), 2.34 (*trans*–isomer, dd, J = 6.6, 2.8 Hz), 2.44 (*trans*–isomer, dd, J = 4.1, 2.8Hz), 4.53 (*cis*–isomer, dd, J = 4.1, 2.8Hz)], 3.35 (*trans*–isomer, dt, J = 10.0, 4.8Hz, 0.72 H), 4.04 (*cis*–isomer, broad m, 0.28H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ *cis*– isomer **133a**: 20.2, 21.4, 26.3, 33.0, 41.0, 68.3, 69.3, 83.7; *trans*–isomer **133b**: 21.8, 25.0, 25.5, 30.3, 35.6, 44.0, 69.7, 73.3, 83.1; exact mass, m/e 152.1201 (calcd for $C_{10}H_{16}O$, m/e 152.1201).

**Base isomerization of alcohols 133a and 133b; *cis*- and *trans*-2-(3-butynyl)-cyclohexanols 119a and 119b**: The potassium salt of 1,3-diaminopropane[111] (KAPA) was prepared at 0°C according to the literature procedure[111] from 1,3-diaminopropane (4 mL) and potassium hydride (24% oil dispersion, 3 mmol). The *cis*- and *trans*-alcohols **133ab** (0.152 g, 1.0 mmol) in hexane (2 mL + 1 mL rinse) were added and the mixture was stirred at 0°C for 1 h. The resulting brown slurry was poured into water (20mL), made acidic with 3 *N* aqueous HCl and extracted with ether (2 x 20mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 8:2 hexane-ethyl acetate gave ($^1$H NMR) a mixture of starting alcohols and the corresponding isomerized alcohols **119a** and **119b**. The yields were not reproducible (24-68%) and depended on temperature and reaction times. The mixture of *cis*- and *trans*- alcohols **119ab** in a ratio ($^1$H NMR) of 1:4, had: IR (neat) 3040-3650, 3400, 2118 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 0.80-2.50 (m, 14H), 1.93 (t, J= 2.4 Hz, 1H), 3.25 (*trans*-isomer, broad m, $J_{1/2}$ =22 Hz, 0.8H), 3.90 (*cis*-isomer, m, $J_{1/2}$ = 7.0Hz, 0.2H); exact mass, m/e 152.1197 (calcd for $C_{10}H_{16}O$, m/e 152.1201).

***Trans*-2-(1-butynyl)cyclohexanol 135**: 1-Butyne (*ca.* 1 mL) was condensed into a 50 mL three-necked flask cooled to -70°C under an argon atmosphere and containing dry THF (20 mL). *n*-Butyllithium (1.29 M in hexane, 5.8 mL, 7.5 mmol) was added dropwise. After a further 10 min at -70°C, boron trifluoride etherate (0.93 mL, 7.5 mmol) was injected followed after another 10 min by cyclohexene oxide (Aldrich, 0.49 g, 0.51 mL, 5 mmol). The reaction mixture was stirred for 30 min at -70°C, quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ether (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 8:2 hexane-ethyl acetate gave pure (TLC, silica, 7:3 hexane-ethyl acetate) **135** (0.62 g, 81%); IR (neat) 3060-3640 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 1.10 (t, J = 7.2 Hz, 3H), 1.00-2.50 (m, 11H), 2.42 (s, 1H), 3.37 (dt, J = 8.5, 4.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 22.6 MHz) $\delta$ 12.3, 14.1, 24.1, 24.7, 31.2, 32.9, 38.8, 73.6, 80.4, 83.8; exact mass, m/e 152.1199 (calcd for $C_{10}H_{16}O$, m/e 152.1201).[130]

**Isomerization of alcohol 135;** ***cis*-** **and** ***trans*-2-(3-butynyl)cyclohexanols 119a and 119b:** The potassium salt of 1,3-diaminopropane (KAPA) (6 mmol) in 1,3-diaminopropane (3 mL) was prepared according to the literature procedure[118] The solution was cooled to 0°C and alcohol **135** (0.1522 g, 1 mmol) in hexane (2 mL + 1 mL rinse) was added and the mixture was stirred for 20 h at 0°C. It was quenched with water and extracted with ether (2 x 10 mL). The combined extracts were dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm) with 8:2 hexane–ethyl acetate gave alcohol **119** (0.051 g, 33%) as a mixture of *cis*- and *trans*-isomers which was identical (TLC, IR, $^1$H NMR) to that obtained by isomerization of alcohols **133a** and **133b** (p. 191).

**5-Bromo-1-pentyne 185:**[161] Bromine (15.98 g, 5.1 mL, 0.1 mol) was added dropwise to a magnetically stirred solution of triphenyl phosphite (343 g, 0.11 mol) in dry ether (50 mL) at 0°C. The orange complex was stirred at 0°C for about 5 min and a solution of 4-pentyne-1-ol[162] (8.41 g, 0.1 mol) and pyridine (8.9 mL, 0.11 mol) in dry ether (25 mL) was added dropwise over *ca.* 10 min. The ice bath was removed and the resulting white slurry was stirred overnight at room temperature. The mixture was poured into water (50 mL) and the product was extracted with ether (2 x 50 mL). The combined extracts were washed with 3 *N* aqueous HCl (30 mL), dried (MgSO$_4$) and concentrated. Distillation of the residue (bp 139–141°C) gave 5-bromo-1-pentyne (9.92 g, 67%) as a colorless, pure (IR, NMR) liquid: IR (neat) 3295, 2111 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 2.03 (m, 3H), 2.25–2.60 (m, 2H), 3.50 (t, J = 6.0 Hz, 2H).

**2-(4-pentynyl)cyclohexanone 140:**[163] Ethylmagnesium bromide (2.19 M in ether, 10 mL, 22 mmol) was added dropwise, under an argon atmosphere to a magnetically stirred solution of *N*-cyclohexylidene–cyclohexanamine **74** (3.59 g, 20 mmol) in dry THF (30 mL). The mixture was refluxed for 18 h and then cooled to room temperature. 5-Bromo-1-pentyne **185** (2.95 g, 20 mmol) in dry THF (2 mL + 1 mL rinse) was added in one portion and the mixture was refluxed for a further 24 h and then cooled to room temperature. The solution was diluted with 3 *N* aqueous HCl (20 mL) and stirred for 48 h. The THF was then evaporated and the residue was extracted with ether (3 x 25 mL). The combined extracts were washed with 3 *N* aqueous HCl (20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residual oil over silica gel (3 x 15 cm) with 9:1 hexane–ethyl acetate gave ketone **140** (1.62 g, 49%) as a pure (TLC, silica, 8:2 hexane–acetate) colorless oil: IR (neat) 3290, 2122, 1706 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.19–1.97 (m, 8H), 1.94 (t, J = 2.5 Hz, 1H), 1.97–2.48 (m, 5H), 2.19 (dt, J = 7.1, 2.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 18.6, 25.0, 26.2, 28.0, 28.8, 34.0, 42.0, 50.3, 68.4, 84.3, 212.6; exact mass, m/e 164.1196 (calcd for $C_{11}H_{16}O$, m/e 164.1201).

*cis*- **and** *trans*-**2-(4–Pentynyl)cyclohexanols 141a and 141b:** A THF solution of lithium aluminum hydride (Aldrich, 1 M in THF, 0.5 mL, 0.5 mmol) was added dropwise to a magnetically stirred solution of ketone **140** (1.37 g, 8.34 mmol) in dry ether (5 mL). Stirring was continued for 10 min at room temperature and the reaction was quenched by dropwise addition of saturated aqueous ammonium chloride (1 mL). The mixture was extracted with ether (2 x 10 mL) and the combined extracts were dried ($MgSO_4$) and evaporated to give an apparently homogeneous (TLC, silica, 8:2 hexane–ethyl acetate) mixture of *cis*– and *trans*–2–(4–pentynyl)cyclohexanols **141a** and **141b** (1.15 g, 83%) in a ratio of 1:1.7 ($^1H$ NMR): IR (neat) 3100–3650, 3310, 2123 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 0.80–2.00 (m, 13H), 1.96 (t, J = 2.5 Hz, 1H), 2.00–2.36 (m, 1H), 2.19 (dt, J = 6.8, 2.8 Hz, 2H), 3.20 (*trans*– isomer, dt, J = 8.8, 4.5 Hz, 0.63H), 3.85 (*cis*– isomer, broad s, 0.37 H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ *trans*– isomer **141b**: 20.6, 24.9, 25.6, 25.8, 30.3, 31.6, 35.8, 44.8, 68.3, 74.5, 84.7; *cis*– isomer **141a**: 18.7, 18.8, 25.2, 26.2, 26.7, 31.1, 33.1, 41.0, 68.3, 69.3, 84.7; exact mass, m/e 148.1240 [calcd for $C_{11}H_{16}$, ($M^{\cdot}-H_2O$), m/e 148.1252].

*cis*- **and** *trans*- **1***H*-**Imidazole–1-carbothioic acid** *O*-**[2-(4–pentynyl)–cyclohexyl] esters 142a and 142b:** Alcohols **141a** and **141b** (0.41 g, 2.47 mmol) and 1,1′–thiocarbonylbisimidazole[137] (0.89 g, 5 mmol) were placed in a flask and covered with dry 1,2–dichloroethane (10 mL). The resulting solution was refluxed under argon for 24 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 7:3 hexane–ethyl acetate gave a pure (TLC, silica, 7:4 hexane–ethyl acetate) mixture (0.505 g, 74%) of **142a** and **142b** in a ratio ($^1H$ NMR) of 1:1.7: IR (neat) 3300, 2121 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.84–2.01 (m, 12H), 1.90 (t, J = 2.3 Hz, 1H), 2.19 (dt, J =

7.1, 2.7 Hz, 2H), 2.28 (m, 1H), 5.29 (*trans*-isomer, dt, J = 10.1, 4.4 Hz, 0.62H), 5.76 (*cis*-isomer, broad s, 0.38H), 7.04 (*trans*-isomer, q, J = 1.0 Hz, 0.62H), 7.06 (*cis*- isomer, q, J = 1.0 Hz, 0.38H), 7.65 (t, J = 1.0Hz, 1H), 8.36 (*trans*-isomer, t, J = 1.0 Hz, 0.62H), 8.37 (*cis*-isomer, t, J = 1.0 Hz, 0.38H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ *trans*- isomer **142b**: 19.0, 24.7, 25.2, 25.8, 30.4, 30.8, 31.3, 41.7, 69.2, 84.5, 87.4, 118.4, 131.2, 137.2; *cis*- isomer **142a**: 21.7, 25.3, 26.3, 28.7, 29.4, 31.6, 37.1, 40.5, 69.2, 83.3, 84.5, 118.3, 131.2, 137.2; exact mass, m/e 276.1289 (calcd for $C_{15}H_{20}N_2OS$, m/e 276.1296).

**Cyclization of alkoxythiocarbonylimidazoles 142a and 142b; *cis*- and *trans*-decahydro-1-methylene-naphthalene 144a and 144b:**[164] The general procedure was followed using the mixture of alkoxythiocarbonylimidazoles **142a** and **142b** (0.166 g, 0.6 mmol) in benzene (40 mL), triphenyltin hydride (0.26 mL, 1.0 mmol) in benzene (10 mL), and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent Kugelrohr distillation [bp 110–165°C (20 mm)] gave a mixture (0.022 g, 24%) of *cis*- and *trans*-decahydro-1-methylene-naphthalene **144a** and **144b** in the ratio ($^1$H NMR) of 1:2. The material was 95% pure (VPC) and had: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.80–1.90 (m, 13H), 2.01 (*trans*- isomer, dt, J = 13.6, 4.5 Hz, 0.66H), 2.00–2.10 (*cis*- isomer, m, 0.33H), 2.10–2.20 (*cis*- isomer, m, 0.33H), 2.34 (*trans*- isomer, dq, J = 12.8, 1.9 Hz, 1.33 H), 2.24–2.38 (*cis*- isomer, m, 0.33H), 4.53 (*trans*- isomer, broad s, 0.66H), 4.60 (*cis*-isomer, broad s, 0.33H), 4.64 (*cis*- and *trans*- isomers, broad q, J = 1.8 Hz, 0.99H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ *trans*- isomer **144b**: 26.5, 26.6, 28.2, 29.1, 34.6, 34.8, 37.2, 44.9, 47.5, 103.8, 153.6.

**Authentic *cis*-decahydro-1-methylene-naphthalene 144a:**[164] *cis*-Octahydro-1(2*H*)-naphthalenone was prepared by PCC oxidation of (1$\beta$, 4a$\alpha$, 8a$\alpha$)-decahydro-1-naphthalenol by a literature procedure[165] and had: IR (neat) 1705 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 100 MHz) $\delta$ 1.00–2.50 (m, 15H), 2.54 (q, J = 4.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 22.9, 23.3, 24.5, 25.1, 29.0, 29.1, 39.0, 40.5, 50.5, 213.2; exact mass, m/e 152.1199 (calcd for $C_{10}H_{16}O$, m/e 152.1201). The ketone was used in the following way: *n*-Butyllithium (1.29 M in hexane, 1.3 mL, 1 mmol) was added dropwise to a magnetically stirred suspension of methyltriphenylphosphonium bromide (Aldrich, 0.3572 g, 1.0 mmol) in dry

THF (5 mL). The orange solution was stirred 15 min at room temperature and the ketone (0.12 g, 0.78 mmol) in THF (2 mL + 1 mL rinse) was added slowly (over *ca.* 2 min). After a further period of 10 min, the yellowish slurry was concentrated and Kugelrohr distillation of the residue [bp 120–130°C (20 mm)] gave pure (99%, VPC) **144a** (0.10 g, 85%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.90–2.40 (m, 16H), 4.52 (*trans-* isomer impurity, q, J = 1.5 Hz, 0.1H), 4.60 (broad s, 0.45H), 4.63 (broad m, 0.47H); $^{13}$C NMR ($CDCl_3$, 22.6 MHz) $\delta$ 22.0, 25.7, 26.9, 27.0, 27.4, 30.9, 32.0, 37.8, 45.5, 106.5, 153.3.

**Authentic *trans-* decahydro-1-methylene–naphthalene 144b:**[164] This authentic sample was prepared by Lu Set. *trans*–Octahydro-1(2*H*)–naphthalenone was made by a literature procedure[165] and contained 82% *trans–* and 18% *cis–* isomers ($^{13}$C NMR). The ketone had: $^{13}$C NMR ($CDCl_3$, 22.6 MHz) $\delta$ 25.2, 25.5, 25.8, 26.5, 33.1, 34.4, 41.8, 45.0, 55.1, 212.6. It was used in the following way: *n*–Butyllithium (1.29 M in hexane, 2.1 mL, 2.75 mmol) was added dropwise to a magnetically stirred suspension of methyltriphenylphosphonium iodide (Aldrich, 1.111 g, 2.74 mmol) in dry THF (10 mL). The orange solution was stirred 15 min at room temperature and the ketone (0.3639 g, 2.4 mmol) in dry THF (10 mL) was added dropwise over *ca.* 5 min. After a further period of 1 h, the yellowish solution was refluxed for 4 h and evaporated. The residue was diluted with ether (50 mL) and the solution was washed with 2 *N* aqueous HCl (10 mL) and saturated aqueous sodium chloride. The solution was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue over silica gel (2 x 15 cm) with hexane gave the apparently pure (VPC) alkene **144b**. The material had: IR (neat) 1690 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.80–1.92 (m, 14H), 2.01 (dt, J = 13.3, 4.5 Hz, 1H), 2.33 (dq, J = 13.1, 1.6 Hz, 1H), 4.51 (q, J = 1.4 Hz, 0.42H), 4.60 (*cis–* isomer impurity, broad s, 0.05H), 4.61 (q, J = 1.9 Hz, 0.53H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 26.5, 26.6, 28.2, 29.1, 34.6, 34.8, 37.2, 44.9, 47.4, 103.8, 153.6; exact mass, m/e 150.1407 (calcd for $C_{11}H_{18}$, m/e 150.1408).

**(5-Iodo-1-pentynyl)benzene 146:**[166] A solution of (5–chloro–1–pentynyl)–benzene[167] (2.32 g, 13 mmol) and anhydrous sodium iodide (6.00 g, 40 mmol) in dry acetone (25 mL) was stirred magnetically and refluxed for 48 h under argon. The mixture was cooled to room temperature and the resulting slurry was extracted with hexane. The solvent was evaporated and the pure ($^1$H NMR) iodide (3.51 g, 100%) was used directly in the next stage. The material had: $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 2.06 (q', J = 6.5 Hz, 2H), 2.55 t, J = 6.4 Hz, 2H), 3.33 (t, J = 6.4 Hz, 2H), 7.08–7.55 (m, 5H). $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 5.3, 20.4, 32.1, 81.7, 87.7, 123.5, 127.7, 128.1, 131.5; exact mass, m/e 270.9938 (calcd for $^{12}C_{10}\,^{13}CH_{11}I$, m/e 270.9939).

**2-(5-Phenyl-4-pentyne)cyclohexanone 147:** Ethylmagnesium bromide was prepared in THF (20 mL) and under argon from magnesium turnings (0.073 g, 3 mmol) and bromoethane (0.327 g, 3 mmol). *N*–Cyclohexylidene–cyclohexanamine **74** (see p. 172) (0.54 g, 3 mmol) in dry THF (2 mL + 1 mL rinse) was added via syringe and with stirring. The mixture was refluxed overnight and then (5–iodo–1–pentynyl)benzene **146** (0.81 g, 3 mmol) in dry THF (2 mL + 1 mL rinse) was injected into the hot mixture. Refluxing was continued for a further 24 h. The mixture was cooled to room temperature and stirred for 30 min with 3 *N* aqueous HCl (10 mL). The solvent was evaporated and the residue was extracted with ether (3 x 25 mL). The combined extracts were washed with 3 *N* aqueous HCl (20 mL), dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 9:1 hexane–ethyl acetate gave pure (TLC, silica, 9:1 hexane–ethyl acetate, ketone **147** (0.45 g, 62%) which had: IR (neat) 1710 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.20–2.50 (m, 12H), 1.62 (t, J = 7.5 Hz, 1H), 2.43 (t, J = 6.6 Hz, 2H), 7.15–7.45 (m, 5H); $^{13}$C NMR (CDCl$_3$, 22.6 MHz) $\delta$ 19.5, 24.8, 26.4, 27.9, 28.8, 33.9, 41.9, 50.2, 80.7, 89.9, 123.9, 127.4, 128.1, 131.4; exact mass, m/e 240.1512 (calcd for $C_{17}H_{20}O$, m/e 240.1514).

***cis*- and *trans*-2-(5–Phenyl-4–pentynyl)cyclohexanols 148a and 148b:** A solution of lithium aluminum hydride (Aldrich, 1 M in THF, 0.07 mL, 0.07 mmol) was injected into a stirred solution of 2–(5–phenyl–4–pentynyl)–cyclohexanone **147** (0.042 g, 0.176 mmol) in dry ether (5 mL). Stirring was continued for 5 min and the reaction was quenched with saturated aqueous ammonium chloride (1 mL). The aqueous phase was removed by pipette and the ether layer was dried (MgSO$_4$) and evaporated to give an apparently homogeneous (TLC, silica 8:2 hexane–ethyl acetate) mixture of *cis*– and *trans*– alcohols **148a and 148b** (0.041 g, 96%) in a ratio ($^1$H NMR) of 1:2: IR (neat) 3130–3630, 2230, 1597

cm$^{-1}$; $^{1}$H NMR (CDCl$_3$, 200 MHz) $\delta$ 0.78–2.04 (m, 14H), 2.40 (t, J = 8 Hz, 2H), 3.21 (*trans*- isomer, broad m, $J_{1/2}$ = 18 Hz, 0.67H), 3.87 (*cis*- isomer, broad m, $J_{1/2}$ = 10 Hz, 0.33H), 7.14–7.44 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ *trans*- isomer **148b**: 19.9, 24.9, 25.6, 26.1, 30.3, 31.7, 35.8, 44.9, 74.6, 80.8, 90.4, 124.2, 127.5, 128.2, 131.6; *cis*- isomer **148a**: 19.7, 20.6, 25.2, 26.4, 26.7, 31.3, 33.2, 41.0, 53.8, 69.4, 90.3, 124.2, 127.5, 128.2, 131.6; exact mass, m/e 242.1663 (calcd for $C_{17}H_{22}O$, m/e 242.1671).

***cis*- and *trans*-1*H*-Imidazole-1–carbothioic acid *O*-[2-(5-phenyl-4–pentynyl) cyclohexyl] esters 149a and 149b:** The mixture of alcohols **148a** and **148b** (0.310 g, 1.28 mmol) and 1,1′–thiocarbonylbisimidazole[137] (0.46 g, 2.6 mmol) were placed in a flask and covered with dry 1,2–dichloroethane (10 mL). The resulting solution was refluxed for 20 h under argon. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 7:3 hexane–ethyl acetate gave the pure (TLC, silica, 7:3 hexane–ethyl acetate, 2 spots) mixture of *cis*- and *trans*- alkoxythiocarbonylimidazoles **149a** and **149b** (0.44 g, 98%) in a ratio ($^{1}$H NMR) of 1:1.7: IR (neat) 2240, 1601 cm$^{-1}$; $^{1}$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.04–2.05 (m, 12H), 2.26 (broad m, 1H), 2.39 (t, J = 7.0Hz, 2H), 5.28 (*trans*- isomer, dt, J = 9.6, 4.6 Hz, 0.63H), 5.76 (*cis*- isomer, broad m, $J_{1/2}$ = 8.0 Hz, 0.37H), 6.90 (*trans*- isomer, dd, J = 1.7, 1.1 Hz, 0.63H); 6.99 (*cis*- isomer, dd, J = 1.5, 1.1 Hz, 0.37H), 7.18–7.40 (m, 5H), 7.56 (*trans*- isomer, t, J = 1.3 Hz, 0.63H), 7.99 (*cis*- isomer, t, J = 1.3 Hz, 0.37H), 8.32 (m, 1H); $^{13}$C NMR (CDCl$_3$, 50.2 MHz) $\delta$ *cis*- isomer **149a**: 21.2, 24.8, 26.1, 28.2, 28.9, 31.3, 40.1, 82.9, 117.6, 123.8, 127.6, 128.2, 130.8, 131.5, 136.7, 183.7; *trans*- isomer **149b**: 19.5, 24.1, 24.6, 25.6, 29.9, 30.3, 31.1, 41.3, 81.1, 86.9, 89.6, 117.6, 123.8, 127.6, 128.2, 130.7, 131.5, 136.9, 183.8; exact mass, m/e 352.1609 (calcd for $C_{21}H_{24}N_2OS$, m/e 352.1609). Anal. Calcd for $C_{21}H_{24}N_2OS$: C, 71.55; H, 6.86; N, 7.98. Found: C, 71.39; H, 6.84; N, 8.04.

**Cyclization of alkoxythiocarbonylimidazoles 149a and 149b; *cis*- and *trans*-decahydro-(*E*)- and (*Z*)-benzylidene–naphthalenes 151ab and 151cd:** The general procedure was followed using the mixture of *cis*- and *trans*- alkoxythiocarbonyl-imidazoles **149a** and **149b** (0.076 g, 0.215 mmol) in benzene (30 mL), triphenyltin hydride (0.14 mL, 0.5mmol) in benzene (10 mL), and AIBN (0.005 g, 0.04 mmol) in the same solvent

(10 mL). Evaporation of the solvent and Kugelrohr distillation [bp 130–180°C (18 mm)] gave a mixture of the four alkenes **151ab** and **151cd** (0.038, 79%) in a ratio (VPC) of 1:7:15:38. The material was >99% pure (VPC) and had: IR (neat) 1598 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.80–3.00 (m, 16H), 6.12 (**151a**, broad s, 0.05H), 6.17 (**151d**, broad s, 0.56 H), 6.20 (**151b**, broad s, 0.12H), 6.31 (**151c**, broad s, 0.27H), 7.06–7.45 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 20.9, 21.4, 25.4, 26.1, 26.3, 26.4, 26.6, 26.7, 27.1, 27.7, 27.9, 28.3, 29.1, 30.4, 30.5, 31.5, 31.6, 31.8, 32.4, 33.4, 34.6, 34.7, 34.8, 35.1, 37.2, 37.3, 38.0, 39.7, 42.5, 45.2, 48.1, 48.3, 48.5, 119.1, 122.1, 122.2, 122.9, 125.7, 125.8, 127.2, 127.6, 128.0, 128.1, 128.7, 128.8, 128.9, 129.0, 137.3, 138.5, 138.7, 139.3, 139.8, 146.0, 146.7, 147.5; exact mass, m/e 226.1724 (calcd for $C_{17}H_{22}$, m/e 226.1721).

**Authentic *cis*- decahydro-(*E*)- and (*Z*)-1–benzylidene–naphthalenes 151ab:** These authentic samples were prepared by Lu Set. *n*–Butyllithium (1.29 M in hexane, 1.5 mL, 1.95 mmol) was added dropwise to a magnetically stirred suspension of benzyltriphenylphosphonium chloride[166] (0.76 g, 1.95 mmol) in dry THF (20 mL). The red solution was stirred for 15 min at room temperature and *cis*–octahydro–1(2*H*)naphthalenone[165] (0.325 g, 2.13 mmol) in dry THF (6 mL) was added dropwise over *ca.* 1 min. After a further period of 3 h the mixture was refluxed for 20 h. The solution was filtered and evaporated. Kugelrohr distillation gave alkenes **151ab** as a mixture of isomers in a ratio ($^1$H NMR) of 1:6.1. The material had $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.00–3.00 (m, 16H), 6.13 (major isomer, broad s, 0.86 H), 6.29 (minor isomer, broad s, 0.14 H), 7.10–7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ major isomer: 26.3, 26.6, 27.8, 29.0, 30.5, 34.8, 35.0, 45.1, 48.4, 119.0, 125.7, 127.9, 129.0, 146.6; minor isomer: 25.5, 25.8, 26.5, 30.4, 33.1, 34.4, 41.8, 45.0, 55.1, 139.2.

**Authentic *trans*- decahydro-(*E*)- and (*Z*)-1–benzylidene–naphthalenes 151cd:** These authentic samples were prepared by Lu Set by the above procedure (see **151ab**) using benzyltriphenylphosphonium chloride[166] (1.196 g, 3.08 mmol) in THF (20 mL), *n*–Butyllithium (1.29 M in hexane, 2.4 mL, 3.1 mmol), *trans*–octahydro–1(2*H*)–naphthalenone[165] (0.4217 g, 2.77 mmol) in THF (10 mL) and a reaction period of 1 h at room temperature and 3 h at reflux. After work up, the material was purified by flash chromatography over silica gel (2 x 15 cm) with hexane. The **alkenes 151cd** (0.069 g, 11%) were obtained as a mixture of (*Z*)- and (*E*)-isomers in a ratio ($^1$H NMR) of 1:6.7. The material had $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.90–1.50 (m, 7H), 1.62–2.04 (m, 7H), 2.97 (broad d, J = 13 Hz, 1H), 6.16 (major isomer, broad s, 0.87H), 6.32 (minor isomer, s, 0.13H), 7.10–7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$, 22.6 MHz) $\delta$ major isomer: 26.3, 26.6, 27.8, 29.0, 30.4, 34.7, 35.0, 45.1, 48.4, 119.0, 125.6, 128.0, 129.0, 146.7.

**2-oxocyclohexanonepropanenitrile 158:**[121] The literature procedure[121] was followed. A solution of enamine **122** (17.65 g, 0.117 mol) and propenenitrile (7.85 g, 0.148 mol) in dry dioxane (60 mL) was refluxed for 21 h under argon. The solvent was evaporated and the residue was suspended in water (10 mL). The product was extracted with ether (3 x 30 mL), and the combined extracts were washed with saturated aqueous ammonium chloride (20 mL), dried ($MgSO_4$) and evaporated. The residue was distilled [bp 128–132°C (25 mm)] [lit.[121] 141–145°C (10 mm)] to afford the pure (TLC, silica, 8:2, hexane–ethyl acetate) ketonitrile **158** (13.39 g, 76%). IR (neat) 2224, 1704 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 1.15–2.75 (m, 1H), 2.43 (t, J = 7.0Hz, 2H); $^{13}$C NMR ($CDCl_3$, 15.1 MHz) $\delta$ 15.2, 25.2, 25.7, 28.0, 34.3, 42.2, 48.9, 119.8, 211.8.

*cis*- **and** *trans*-**1***H*-**Imidazole-1-carbothioic acid** *O*–**[2–(2–cyanoethyl)–cyclohexyl] esters 160a and 160b:**

**a)** *cis*- **and** *trans*-**2-Hydroxycyclohexanepropanenitriles 158a and 158b**: A solution of ketonitrile **158** (1.10 g, 7.3 mmol) in THF (10 mL) was added dropwise over *ca.* 15 min at 0°C to a stirred suspension of sodium borohydride (0.56 g, 14.6 mmol) in THF (20 mL).[123] The temperature was kept at 0–5°C for 1.5 h and the mixture was then acidified at 0°C to pH 1 with 6 N HCl. The solvent was evaporated and the residue was dissolved in water (10 mL) and extracted with ether (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give the crude alcohols in quantitative yield: IR (neat) 3160–3700, 3000–3440, 2250 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 0.80–2.20 (m, 12H), 2.37 (broad t, J = 6.2 Hz, 2H), 3.25 (*cis*- isomer, broad m, 0.5H), 3.75 (*trans*- isomer, broad m, 0.5H).

**b) Alkoxythiocarbonylimidazoles 160a and 160b**: The mixture of alcohols **159a** and **159b** (1.00 g, 6.52 mmol) and 1,1'-thiocarbonylbisimidazole[117](2.30 g, 13 mmol) were placed in a flask and covered with dry dichloromethane (10 mL). The resulting solution was refluxed overnight under argon. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 1:1 hexane–ethyl acetate gave a mixture of *cis*-and *trans*- alkoxythiocarbonylimidazoles **160a** and **160b** (1.90 g, 99%) in a ratio (NMR) of 1:27 as a pure (TLC, silica, 7:3 hexane–ethyl acetate) oil. The material had IR (neat) 2225 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.10–2.10 (m, 10H), 2.20–2.55 (m, 3H), 5.34 (*trans*- isomer, dt, J = 9.6, 4.2 Hz, 0.73H), 5.85 (*cis*- isomer, broad s, 0.27H), 7.09 (broad s, 1H), 7.64 (*cis*- isomer, broad s, 0.27H), 7.67 (*trans*- isomer, broad s, 0.73H), 8.37(*cis*- isomer, broad s, 0.27H), 8.40 (*trans*- isomer, broad s, 0.73H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz), $\delta$ *trans*- isomer: 14.8, 24.0, 24.4, 27.9, 29.6, 30.3, 40.7, 86.0, 117.2, 119.2, 130.7, 136.9, 183.5; *cis*- isomer: 20.9, 27.1, 27.4, 28.9, 29.3, 39.3, 81.5, 117.2, 119.2, 130.7, 136.6, 183.5; exact mass, m/e 263.1089 (calcd for $C_{13}H_{17}N_3OS$, m/e 263.1092); Anal. Calcd for $C_{13}H_{17}N_3OS$: C, 59.28; H, 6.51; N, 15.96. Found: C, 58.88; H, 6.56; N, 15.66.

**Cyclization of 160a and 160b; octahydro-1*H*-inden-1-one 162:**[123] The general procedure was followed using a mixture of **160a** and **160b** (0.118 g, 0.45 mmol) in benzene (40 mL), triphenyltin hydride (0.14mL, 0.6 mmol) in benzene (10 mL), and AIBN (0.010 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was stirred for 1 h with 80% v/v aqueous acetic acid (3 mL) and evaporated. The residue was then suspended in hexane (50 mL) and dried over anhydrous potassium carbonate for 1 h (stirring). The solution was filtered and evaporated. Kugelrohr distillation [bp 80–100°C(1.0 mm)] followed by flash chromatography over silica gel (1.5 x 15 cm) with 8:2 hexane–ethyl acetate, gave pure (TLC, silica, 8:2 hexane–ethyl acetate), bicyclic ketone **162** (low Rf, 0.042g, 68%) and pure (TLC, silica, 8:2 hexane–ethyl acetate) cyclohexanepropanenitrile **163** (high Rf, 0.008 g, 11.0%). The octahydro-1*H*-inden-1-one **162** had: IR (neat)1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.80–2.40 [m, 14H, including: 2.24 (dd, J =9.8, 6.8 Hz)]; $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 24.9, 25.5, 25.8, 27.6, 32.6, 37.0, 43.3, 55.6, 218.6; exact mass, m/e 138.1042 (calcd or $C_9H_{14}O$, m/e 138.1045), Anal. Calcd for

$C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 76.81; H, 10.08. The material had physical properties very close (IR, $^1H$ NMR) to those reported in the literature.[123] The cyclohexanepropanenitrile **163** had: IR (neat) 2225 cm$^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.92 (m, 2H), 1.10–1.48 (m, 4H), 1.56 (q, J = 7.9 Hz, 2H), 1.64–1.82 (m, 5H), 2.37 (t, J = 7.7 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ 14.7, 26.0, 26.4, 32.6, 36.7, 128.4; exact mass, m/e 137.1186 (calcd for $C_9H_{15}N$: m/e 137.1204). The material was identical (VPC, TLC, IR, $^1H$ NMR, $^{13}C$ NMR) with an authentic sample.

**Authentic cyclohexanepropanenitrile 163:**[169]

**a) Cyclohexanepropanenitrile tosyl hydrazone.**[170] The ketonitrile **158** (1.00 g, 6.61 mmol) and *p*–toluenesulfonyl hydrazide (1.35 g, 7.3mol) in absolute ethanol (2 mL) were stirred at 80°C for 1 h. The mixture was cooled to room temperature and the crystalline product was collected and recrystallized from 95% ethanol. The resulting hydrazone (1.86 g, 88%) was suitable for the next stage.

**b) Cyclohexanepropanenitrile 163:** Sodium borohydride (0.55 g, 14.55 mmol) was dissolved in acetic acid (21 mL) at 0°C. The hydrazone (1.86 g, 5.82 mmol) was added[169] with stirring and the ice bath was removed. Stirring was continued for 1 h (during which time the mixture attained room temperature) and then for 2 h at 70°C (oil bath). The mixture was poured onto ice, made basic by addition of solid sodium hydroxide, extracted with hexane and dried ($MgSO_4$). The solvent was evaporated and flash chromatography of the residue over silica gel (2 x 15 cm) with 8:2 hexane–ethyl acetate gave pure (TLC, silica, 8:2 hexane–ethyl acetate) nitrile **163**: IR (neat) 2225 cm$^{-1}$; $^1H$ MR ($CDCl_3$, 80 MHz) $\delta$ 0.90–1.80 (m, 13H), 2.35 (t, J = 7.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) $\delta$ 14.5, 26.0, 26.3, 32.3, 36.4, 128.1.

**1-(1-Cyclopenten-1-yl)pyrrolidine 186:**[121] The procedure for **122**[121] was followed using cyclopentanone (29.82 g, 0.354 mol), pyrrolidine (25.21 g, 0.354 mol), benzene (100 mL), and a reaction period of 2 h. Distillation of the crude product [bp 102–104°C (18 mm)] [lit.[121] bp 81–83°C (9 mm)] gave the pure enamine **186** (40.55 g, 83%). The IR spectrum showed no carbonyl absorption.

**2-Oxocyclopentanepropanenitrile 164:**[121] The procedure[121] for **158** was followed using cyclopentanone enamine **186** (19.00 g, 0.1385 mol) and propenenitrile (9.19 g, 0.173 mol) in dry dioxane (70 mL). The pure ketonitrile ($^1$H NMR, $^{13}$C NMR) (12.24 g, 64%) had: bp 130−131°C(4.5 mm)[lit.[121] bp 144−147°C (13 mm)]; IR (neat) 2225, 1730 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.35−2.60 (m, 9H), 2.50 (t, J = 6.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 15.4, 20.5, 25.6 29.4, 37.8, 47.6, 119.5, 219.4.

*cis*- **and** *trans*- **1*H*-Imidazole-1−carbothioic acid *O*-[2-(2−cyanoethyl)−cyclopentyl] esters 166a and 166b:**

**a)** ***cis*- and *trans*- 2-Hydroxycyclopentanepropanenitriles 187a and 187b:** The procedure[122] for **159** was followed using ketonitrile **164** (1.00 g, 7.3mmol) in THF (10 mL) and sodium borohydride (0.56 g, 14.6 mmol) in THF (20 mL). The crude mixture of *cis*− and *trans*− alcohols (0.90 g, 88%) was used directly for the next step. The material had: IR (neat) 3040−3700, 2250 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 0.85−2.20 (m, 10H), 2.43 (broad t, J = 6.0 Hz, 2H), 3.75 (broad m, 0.67H), 4.15 (broad s, 0.33H).

**b) Alkoxythiocarbonylimidazoles 165a and 165b:** The mixture of *cis*− and *trans*− alcohols **187a** and **187b** (0.90 g, 6.47 mmol) and 1,1'−thiocarbonylbisimidazole[137] (2.14 g, 12 mmol) were placed in a flask and covered with dry dichloromethane (15mL). The resulting solution was refluxed for 24 h under argon. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 7:4 hexane−ethylacetate gave a mixture of alkoxythiocarbonylimidazoles **165a** and **165b** (1.44 g, 89%) in a ratio ($^1$H NMR) of 1:8.2 as a pure (TLC, silica, 2 spots, 7:4 hexane−ethyl acetate) oil. The material had: IR (neat) 2225 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.39 (dq, J = 13.2, 8.0 Hz, 1H), 1.50−2.36 (m, 7H), 3.37−3.50 (m, 1H), 3.48 (t, J = 7.6 Hz, 2H), 5.52 (major isomer, dq, J = 3.9, 3.2 Hz, 0.85H), 5.94 (minor isomer, dt, J = 4.2, 1.35 Hz, 0.15H), 7.70 (broad s, 1H), 7.61 (minor isomer, t, J = 2.2 Hz, 0.15H), 7.65 (major isomer, t, J = 2.2 Hz, 0.85 H), 8.33 (minor isomer, broad s, 0.15H), 8.36 (major isomer, broad s, 0.85H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ *trans*− isomer **165b**: 16.4, 23.4, 29.4, 30.4, 31.9, 44.9, 90.5, 118.3, 119.6, 131.3, 137.3, 184.0; *cis*− isomer **165a**: 32.6, 36.9, 44.4, 87.9; exact mass, m/e 249.0936 (calcd for $C_{12}H_{15}N_3OS$, m/e 249.0936).

**Cyclization of alkoxythiocarbonylimidazoles 165a and 165b; hexahydro-2(1*H*)–pentalenone 166**[124]**and cyclopentanepropanenitrile 167:** The general procedure was followed using the mixture of **165a** and **165b** (0.166 g, 0.668 mmol) in benzene (40 mL), triphenyltin hydride (0.25 mL, 1.0 mmol) in benzene (10 mL), and AIBN (0.01 g, 0.07 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was stirred for 1 h with 80% v/v aqueous acetic acid (3 mL) and evaporated. The residue was suspended in hexane (50 mL) and dried over anhydrous potassium carbonate for 1 h (stirring). The solution was filtered and evaporated. Kugelrohr distillation [bp 160–200°C(17 mm)] gave an oil (0.033 g, 39% combined yield) of which 45% (VPC) was hexahydro-2(1*H*)–pentalenone **166** and 52% (VPC) was cyclopentanepropaneitrile **167**. The compounds were identified by the spectral properties of the mixture: IR (neat) 2226 cm$^{-1}$ (**167**), 1733 cm$^{-1}$ (**166**); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.76–2.86 [m, including 0.90 (m), 1.14 (m), 1.46 (m, J = 6.8 Hz), 1.70 (q, J = 7.3Hz), 1.93 (m, J = 7.7 Hz), 2.29 (d, J = 8.5 Hz), 2.38 (**167**, t, J = 7.7 Hz), 2.58 (dt, J = 9.5, 4.6 Hz), 2.81 (m)]; $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ **166**: 26.3, 26.5, 29.9, 33.6, 38.0, 41.2, 52.2, 223.4; $\delta$ **167**, 16.5, 25.2, 31.7, 32.6, 39.4, 128.4; exact mass, m/e 124.0889 (calcd for $C_8H_{12}O$, m/e 124.0880). The spectral characteristics for **166** were identical with those reported in the literature.[124]

**1-(1-Cyclohepten-1-yl)pyrrolidine 188:**[171] The procedure for **122**[133] was followed using cycloheptanone (7.12 g, 63.5 mmol), pyrrolidine (5.00 g, 70 mmol), benzene (50 mL) and a reaction period of 2 h. Distillation of the crude product [bp 93–95°C (2.2 mm)] gave the pure enamine **188** (5.30 g, 50%): IR (neat) 1623 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.25–2.75 (m, 14H), 2.80–3.15 (broad t, J = 7.0 Hz, 4H), 4.15–4.80 (broad m, 1H).

**2-Oxocycloheptanepropanenitrile 168:** The procedure for **158**[121] was followed using cycloheptanone enamine **188** (5.26 g, 0.0318 mol) and propenenitrile (2.62 mL, 0.04 mol) in dry dioxane (20 mL). The pure (TLC, silica, 8:2 hexane–ethyl acetate) ketonitrile **168** (4.82 g, 92%) had: bp 135–145°C (1.0 mm); IR (neat) 2250, 1700 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 80 MHz) $\delta$ 1.00–2.20 (m, 9H), 2.25–3.00 (m, 6H); $^{13}$C NMR (CDCl$_3$, 15.1 MHz) $\delta$ 15.2, 23.7, 27.6, 28.8, 29.0, 31.6, 43.4, 50.0, 119.5, 214.2; exact mass, m/e 165.1161 (calcd for $C_{10}H_{15}N$, m/e 165.1154).

***cis*- and *trans*-1*H*-Imidazole-1–carbothioic acid *O*-[2-(2–cyanoethyl)cycloheptyl] esters 169a and 169b:**

**a) *cis*- and *trans*-2-Hydroxycycloheptanepropanenitriles 189a and 189b**: The procedure[122] for **159** was followed using ketonitrile **168** (1.21 g, 7.3 mmol) in THF (10 mL) and sodium borohydride (0.56 g, 14.6 mmol) in THF (20 mL). The crude mixture of *cis*– and *trans*– alcohols was used directly for the next step.

**b) Alkoxythiocarbonylimidazoles 169a and 169b**: The above mixture of *cis*– and *trans*– alcohols and 1,1'–thiocarbonylbisimidazole[137] (2.32 g, 13 mmol) were placed in a flask and covered with dry dichloromethane (25 mL). The resulting solution was refluxed for 24 h under argon. Evaporation of the solvent and flash chromatoraphy of the residue over silica gel (2 x 15 cm) with 1:1 hexane–ethyl acetate gave a mixture of alkoxythiocarbonylimidazoles **169a** and **169b** (1.49 g, 74% overall from ketonitrile) in a ratio ($^1$H NMR) of 1:3.5 as a pure (TLC, silica, 2 spots, 7:4 hexane–ethyl acetate) oil. The material had: IR (neat) 2224 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.38–2.20 (m, 13H), 2.30–2.52 (m, 2H), 5.43 (minor isomer, ddd, J = 9.6, 7.2, 3.5 Hz, 0.22H), 5.80 (major isomer, q', J = 3.4 Hz, 0.78H), 7.01 (broad s, 1H), 7.58 (major isomer, broad s, 0.78H), 7.62 (minor isomer, broad s, 0.22H), 8.30 (major isomer, broad s, 0.78H), 8.36 (minor isomer, broad s, 0.22H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ major isomer: 15.4, 22.2, 26.1, 27.5, 28.5, 28.7, 30.7, 41.9, 85.3, 117.8, 119.1, 131.0, 136.7, 183.6; minor isomer: 15.1, 22.5, 26.2, 28.9, 29.5, 31.5, 42.7, 88.4, 116.6, 119.2, 137.0, 183.6, exact mass, m/e 277.1255 (calcd for $C_{14}H_{19}N_3OS$, m/e 277.1249).

**Cyclization of alkoxythiocarbonylimidazoles 169a and 169b; Octahydro–(2*H*)-azulen-1–ones 170ab:**[172] The general procedure was followed using the mixture of alkoxythiocarbonylimidazoles **169a** and **169b** (0.154 g, 0.5566 mmol) in benzene (40 mL), triphenyltin hydride (0.19 mL, 0.75 mmol) in benzene (10 mL), and AIBN (0.005 g, 0.04 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was stirred for 1 h with 80% v/v aqueous acetic acid (3 mL) and evaporated. The residue was suspended in hexane (50 mL) and dried over anhydrous potassium carbonate for 1 h (stirring). The solution was filtered and evaporated. Kugelrohr distillation [bp 85–100°C (0.6 mm)] gave an oil **170** (0.065 g, 77%) that was 97% pure (VPC) and consisted of a mixture of isomers in a ratio (VPC) of 1:23.4. Cycloheptanepropanenitrile **171** (2.5%, VPC) was also identified (IR) in the reaction product. The mixture **170** had: IR (neat) 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 1.80–2.70 (m, 16H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ major isomer: 26.8, 27.0, 27.6, 28.2, 28.8, 35.4, 38.0, 43.7, 55.4, 221.2; minor isomer: 26.9, 29.2, 31.5, 33.0, 37.9, 41.4, 53.0, 222.0; exact mass, m/e 152.1203 (calcd for $C_{10}H_{16}O$, m/e 152.1201); Anal. Calcd for $C_{10}H_{16}O$: C, 78.9; H, 10.60. Found: C, 78.86, H, 10.69. The IR and mass spectra of **170ab** have been reported in the literature.[172] Cycloheptanepropanenitrile **171** had: IR (neat) 2225$cm^{-1}$.

**4-(1-Butyl-1-pentenyl)-(*E*)-morpholine 190:** 5-Nonanone (2.85 g, 0.02 mol) and freshly distilled morpholine (6.10 g, 0.07 mol) in dry benzene (30 mL) were cooled to 0°C under argon. Titanium tetrachloride (1.21 mL, 0.011 mol) in benzene (20 mL) was added dropwise over 20 min and the mixture was stirred for 20 h at room temperature. The resulting slurry was filtered by suction through a pad of Celite (2 x 4 cm) and the solvent was evaporated. Kugelrohr distillation [bp 105–115°C (0.9 mm)] of the residue gave the enamine **190** (3.39 g, 80%): IR (neat) 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.90 (broad t, J = 7.0 Hz, 6H), 1.40–1.75 (m, 6H), 1.83–2.33 (m, 4H), 2.65–3.97 (m, 4H), 3.63 (m, 4H), 4.39 (t, J = 7.2 Hz, 1H). The material[173] which was pure as judged by the good quality of the integrated $^1H$ NMR spectrum, was used immediately for the next stage.

**5-Oxo-4-propylnonanenitrile 172:** A solution of enamine **190** (3.30 g, 15.6 mmol) and propenenitrile (1.03 g, 19.5mmol) in dioxane (20 mL) was refluxed for 21 h under argon. The solvent was evaporated and Kugelrohr distillation of the residue [bp 115–125°C (0.3 m)] gave the ketonitrile **172** as a colorless oil (0.91 g, 38%). Trace impurities were detectable by TLC (silica, 8:2 hexane–ethyl acetate). THe material had: IR (neat) 2230, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.90 (broad t, J = 6.0 Hz, 6H), 1.10–2.95 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 15.1 MHz) $\delta$ 13.8, 14.1, 15.3, 20.2, 22.4, 23.6, 25.7, 26.1, 33.7, 42.4, 119.3, 213.0; exact mass, m/e 195.1625 (calcd for $C_{12}H_{21}NO$, m/e 195.1623).[121]

***Threo*- and *erythro*-5-Hydroxy-4-propylnonanenitrile 191:** Sodium borohydride (0.150 g. 4.0 mmol) was added to a solution of ketonitrile **172** (0.91 g. 4.66 mmol) in 95% ethanol (20 mL).[122] The mixture was stirred for 3 h at room temperature (TLC control) and evaporated. The residue was acidified with 3 *N* aqueous HCl and extracted with ether (3 x 15 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give the crude product **191** (0.54 g. 58%) which was used without further purification. The material had IR (neat) 3100–3680, 2228 $cm^{-1}$; $^1H$ MR ($CDCl_3$, 80 MHz) $\delta$ 0.91 (broad t, 6H), 0.90–2.00 (m, 9H), 2.20–3.10 (m, 5H), 3.50–3.95 (m, 0.75H), 4.00–4.35 (m, 0.25H).

***threo*- and *erythro*-1*H*-Imidazole-1-carbothioic acid *O*–(1–cyano–3–propyl–oct–4–yl) esters 173:** The crude mixture of alcohols **191** (0.54 g, 2.73 mmol) and 1,1'–thiocarbonylbisimidazole[137] (0.97 g, 5.4 mmol) were placed in a flask and covered with dry dichloromethane (15 mL). The resulting solution was refluxed for 20 h under argon. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 1:1 hexane–ethyl acetate gave a mixture of alkoxythiocarbonylimidazoles **173** (0.112 g, 13%) in a ratio ($^1H$ NMR) of 1:1 as a pure (TLC, silica, 7:4 hexane–ethyl acetate) oil. The material had: IR (neat) 2230 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.92 (t, J = 7.7 Hz, 2H), 0.93 (t, J = 6.4 Hz, 2H), 0.98 (t, J = 6.4 Hz, 2H), 1.20–1.64 (m, 8H), 1.72 (m, 1H), 1.75 (q, J = 6.5 Hz, 2H), 1.91 (m, 1H), 2.03 (m, 1H), 2.50 (m, 2H), 5.76 (m, 1H), 7.07 (s, 1H), 7.62 (s, 1H), 8.33 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 13.9, 14.3, 15.6, 20.3, 20.4, 22.5, 25.9, 27.6, 27.8, 29.8, 29.9, 31.6, 39.9, 85.4, 85.5, 117.8, 119.1, 131.0, 136.8, 184.1; exact mass, m/e 307.1719 (calcd for $C_{16}H_{25}N_3OS$, m/e 307.1718); Anal. Calcd for $C_{16}H_{25}N_3OS$: C, 62.50, H, 8.20; N, 13.67. Found: C, 62.70; H, 8.47; N, 13.27.

**Cyclization of alkoxythiocarbonylimidazoles 173; *trans*-2–butyl-3–propyl-cyclopentanone 174:**[125] The general procedure was followed using alkoxythiocarbonyl–imidazoles **173** (0.162 g, 0.528 mmol) in benzene (40 mL), triphenyltin hydride (0.18 mL, 0.7 mmol) in benzene (10 mL), and AIBN (0.005 g, 0.04 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was stirred for 1 h with 80% v/v aqueous acetic acid (3 mL) and evaporated. The residue was suspended in hexane (50 mL) and dried over anhydrous potassium carbonate for 1 h (stirring). The solution was filtered and

evaporated. Kugelrohr distillation [bp 90–110°C (0 mm)] gave cyclopentanone **174** (0.071 g, 74.3%) of 97% (VPC) purity: IR (neat) 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.90 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.1Hz, 3H), 1.17–1.75 (m, 12H), 1.80–1.94 (m, 1H), 2.02–2.20 (m, 2H), 2.26–2.38 (ddt, J = 17.0, 8.0, 1.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ 13.9, 14.3, 20.3, 23.0, 27.0, 27.9, 29.1, 37.1, 37.9, 41.4, 55.0, 221.4; exact mass, m/e 182.1673 (calcd for $C_{12}H_{22}O$, m/e 182.1671).

*threo*-**Bromo(5-hydroxy-4-octyl)mercury 192:** A general literature procedure[13] was followed using (*Z*)-4-octene (Chemical Samples Co., 2.00 g, 17.8 mmol, 95%), mercuric acetate (5.68 g, 17.8 mmol) and water (10 mL) in THF (30 mL). The crude product (4.26 g, 61%) had: IR (neat) 3100–3700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.95 (broad t, J = 7.2 Hz, 6H), 1.20–2.25 (m, 8H), 2.65–3.05 (m, 2H), 4.10 (dt, J = 6.0, 3.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 22.6 MHz) $\delta$ 14.0, 19.2, 25.5, 35.3, 42.4, 68.7, 75.2.

*threo*- **and** *erythro*-**5-Hydroxy-4-propyloctanenitrile 177:** Sodium trimethoxyborohydride[174] (1.25 M in THF, 20 mL, 25 mmol) was added dropwise at room temperature over 6.5 h to a solution of mercurial **192** (1.80 g, 4.39 mmol) and propenenitrile (8.6 mL, 130 mmol) in dry dichloromethane (15 mL).[13] The mixture was stirred for 20 h at room temperature and the resulting slurry was filtered by suction through a pad of Celite (2 x 4 cm) and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 7:4 hexane–ethyl acetate gave the pure (TLC, silica, 7:4 hexane–ethyl acetate) hydroxynitrile **177** as a mixture of isomers (0.435 g, 54%): IR (neat) 3100–3700, 2227 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 0.90 (broad t, 6H), 1.00–2.10 (m, 12H), 2.40 (t, J = 7.4 Hz, 2H), 3.60 (broad m, 1H); $^{13}C$ NMR ($CDCl_3$, 50.3 MHz) $\delta$ isomer *a* 14.0, 15.5, 19.5, 20.1, 25.2, 32.2, 36.9, 42.1, 72.8, 120.2; isomer *b*: 14.3, 15.3, 19.2, 20.6, 26.1, 31.1, 35.4, 42.3, 72.7, 120.1; exact mass, m/e 183.1617 (calcd for $C_{11}H_{21}NO$, m/e 183.1623).

*threo*- **and** *erythro*-**1*H*-Imidazole-1–carbothioic acid *O*-(1–cyano-3–propylhept-4-yl) esters 178:** The mixture of hydroxynitriles **177** (0.36 g, 1.96 mmol) and 1,1'–thiocarbonylbisimidazole[137] (0.70 g, 3.9 mmol) were placed in a flask and covered with dry dichloromethane (15 mL). The resulting solution was refluxed for 20 h under argon.

Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 7:4 hexane—ethyl acetate gave the pure (TLC, silica, 7:4 hexane—ethyl acetate) alkoxythiocarbonylimidazoles **178**(0.52 g, 90%): IR (neat) 2228 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.93 (t, J = 7.1 Hz, 1.4H), 0.97 (t, J = 6.5 Hz, 3.0H), 0.98 (t, J = 6.5 Hz, 1.6H), 1.24—1.58 (m, 6H), 1.62—1.78 (m, 2H), 1.80—2.06 (m, 3H), 2.38—2.58 (m, 2H), 5.68—5.80 (m, 1H), 7.04 (broad t, J = 0.8 Hz, 1H), 7.59 (broad s, 1H), 8.30 (broad s, 1H); $^{13}$C NMR (CDCl$_3$, 50.32 MHz) $\delta$ 13.9, 14.2, 15.6, 18.8, 19.0, 20.3, 20.4, 26.0, 31.7, 31.8, 32.2, 32.4, 39.9, 40.0, 85.2, 85.3, 117.8, 118.9, 131.0, 136.8, 184.1; exact mass, m/e 293.1563 (calcd for $C_{15}H_{23}N_3OS$, m/e 293.1562); Anal. Calcd for $C_{15}H_{23}N_3OS$: C, 61.40; H, 7.90; N, 14.32. Found: C, 61.23; H, 7.93; N, 14.34.

**Cyclization of alkoxythiocarbonylimidazoles 178; *trans*-2, 3-dipropylcyclopentanone 179:**[175] The general procedure was followed using a mixture of the alkoxythiocarbonylimidazoles **178** (0.105 g, 0.36 mmol) in benzene (40 mL), triphenyltin hydride (0.10 mL, 0.41 mmol) in benzene (10 mL), and AIBN (0.005 g, 0.04 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was stirred for 1 h with 80% v/v aqueous acetic acid (3 mL) and evaporated. The residue was suspended in hexane (50 mL) and dried over anhydrous potassium carbonate for 1 h (stirring). The solution was filtered and evaporated. Kugelrohr distillation [bp 90—110°C(0.4 mm)] gave cyclopentanone **179** (0.044 g, 73%) which was > 99% pure (VPC) and had: IR (neat) 1741 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.90 (t, J = 7.0Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H), 1.20—1.58 (m, 8H), 1.60—1.74 (m, 2H), 1.84 (m, 1H), 2.01—2.21 (m, 2H), 2.34 (ddt, J = 16.0, 8.8, 1.5 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) $\delta$ 14.3, 14.4, 20.2, 20.3, 27.1, 30.5, 37.1, 37.9, 41.5, 54.9, 221.5; exact mass, m/e 168.1519 (calcd for $C_{11}H_{20}O$, m/e 168.1514); Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.34; H, 12.11.

## V. REFERENCES

1. Tedder, J. M. *Angew. Chem. Int. Ed. Engl.* 1982, 401; Tedder, J.M.; Walton, J.C. *Tetrahedron*, 1980, **36**, 701; Tedder, J.M.; Walton, J.C. *Adv. Phys. Org. Chem.* 1978, **16**, 86; Tedder, J.M.; Walton, J.C. *A.C.S. Symposia* 1978, **66**, 107; Tedder, J.M.; Walton, J.C. *Accounts Chem. Res.* 1976, **9**, 183.
2. Carona, T.; Cittero, A.; Ghirardini, M.; Minisci, F. *Tetrahedron*, 1977, **33**, 793.
3. Hoyland, J.R. *Theor. Chim. Acta*, 1971, **22**, 229.
4. Whitesides, G.M.; Hill, C.L. *J. Am. Chem. Soc.* 1974, **96**, 870; Jensen, F.R.; Miller, J.J.; Cristol, S.J.; Beckley, R.S. *J. Org. Chem.* 1972, **37**, 4341.
5. Giese, B.; Meister, J. *Chem. Ber.* 1977, **110**, 2588.
6. Giese, B.; Kretzschmar, G.; Meixner, J. *Chem. Ber.* 1980, **113**, 2787; Giese, B.; Meixner, J. *Angew. Chem. Int. Ed. Engl.* 1980, **19**, 206; Giese, B.; Meixner, J. *Chem. Ber.* 1981, **114**, 2138. Giese, B.; Dupuis, J.; Hasskerl, T.; Meixner, J. *Tetrahedron Lett.* 1983, 703.
7. Giese, B.; Heuck, K. *Chem. Ber.* 1979, **112**, 3759; Giese, B.; Heuck, K. *Tetrahedron Lett.* 1980, 1829.
8. Giese, B.; Heuck, K. *Chem. Ber.* 1981, **114**, 1572.
9. Giese, B.; Heuck, K.; Luning, U. *Tetrahedron Lett.* 1981, 2155.
10. Giese, B.; Zwick, W. *Chem. Ber.* 1982, **115**, 2526; Giese, B.; Gonzalez Gomez, J.A. *Tetrahedron Lett.* 1982, 2765; Giese, B.; Horler, H.; Zwick, W. *Tetrahedron Lett.* 1982, 931; Giese, B.; Zwick, W. *Chem. Ber.* 1983, **116**, 1264.
11. Giese, B.; Kretzschmar, G. *Chem. Ber.* 1982, **115**, 2[illegible]12.
12. Giese, B.; Erfart, U. *Chem. Ber.* 1983, **116**, 1240.
13. Kozikowski, A.P.; Nieduzak, T.R.; Scripko, J. *Organometallics*, 1982, **1**, 675.
14. Kozikowski, A.P.; Scripko, J. *Tetrahedron Lett.* 1983, 2051.
15. Danishefsky, S.; Taniyama, E.; Webb II, R.R. *Tetrahedron Lett.* 1983, 11.
16. Burke, S.D.; Fobare, W. F.; Armistead, D.M. *J. Org. Chem.* 1982, **47**, 3348.
17. Kosugi, M.; Kurino, K.; Takayama, K.; Migita, T.J. *Organomet. Chem.* 1973, **56**, C11; Keck, G.E.; Yates, J.B. *J. Am. Chem. Soc.* 1982, **104**, 5829.
18. Webb II, R.R.; Danishefsky, S. *Tetrahedron Lett.* 1983, 1357.
19. Julia, M. *Rec. Chem. Prog.* 1964, **25**, 3; Julia, M. *Pure and Applied Chem.* 1967,

**15**, 167; Julia, M. *Accounts Chem. Res.* 1971, 386; Julia, M. *Pure and Applied Chem.* 1974, 553; Beckwith, A.L.J. *Tetrahedron*, 1981, **37**, 3073.

20. Butler, G.B., Angelo, R.J. *J. Am. Chem. Soc.* 1957, **79**, 3128; Marvel, C.S.; Vest, R.D. *J. Am. Chem. Soc.* 1957, **79**, 5771.
21. Lamb, R.C.; Ayers, P.W.; Toney, M.K. *J. Am. Chem. Soc.* 1963, **85**, 3483.
22. Walling, C.; Pearson, M.S. *J. Am. Chem. Soc.* 1964, **86**, 2262.
23. Julia, M.; Surzur, J.M.; Katz, L. *Bull. Soc. Chim.Fr.* 1964, 1109.
24. Julia, M.; Surzur, J.-M., Katz, L.; LeGoffic, F. *Bull. Soc. Chim. Fr.* 1964, 1116; Julia, M.; Le Goffic, F.; Katz, L. *Bull. Soc. Chim. Fr.* 1964, 1122.
25. Julia, M.; Le Goffic, F. *Bull. Soc. Chim. Fr.* 1964, 1129.
26. Julia, M.; Maumy, M.; Mion, L. *Bull. Soc. Chim. Fr.* 1967, 2641; Julia, M.; Maumy, M. *Bull. Soc. Chim. Fr.* 1969, 2415.
27. Julia, M.; Maumy, M. *Bull. Soc. Chim. Fr.* 1969, 2427.
28. Capon, B.; Rees, C.W. *Annu. Rep. Progr. Chem.* 1964, **61**, 261.
29. Julia, M.; Maumy, M. *Bull. Soc. Chim. Fr.* 1968, 1603.
30. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* 1972, **94**, 6064; Pines, H., Sih, N.C.; Rosenfield, D.B. *J. Org. Chem.* 1966, **31**, 2255.
31. Breslow, R.; Olin, S.S.; Groves, J.T. *Tetrahedron Lett.*, 1968, 1837.
32. Sam, T.W.; Sutherland, J.K. *J. Chem. Soc.; Chem. Commun.* 1971, 970.
33. Menapace, L.W.; Kuivila, H.G. *J. Am. Chem. Soc.* 1964, **86**, 3047.
34. Beckwith, A.L.J. *Tetrahedron*, 1981, **37**, 3073.
35. Walling, C.; Cooley, J.H.; Ponaras, A.A.; Racah, E.J. *J. Am. Chem. Soc.* 1966, **88**, 5361.
36. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.*, 1972, **94**, 6059.
37. Capon, B.; Rees, C.W. *Annual Reports*, 1964, **61**, 261; Capon, B. *Quart. Rev.* 1964, **18**, 45; Rieke, R.D.; Moore, N.A. *Tetrahedron Lett.* 1969, 2035; Rieke, R.D.; Moore, N.A. *J. Org. Chem.* 1972, **37**, 413.
38. Bischof, P. *Tetrahedron Lett.* 1979, 1291; Bischof, P. *Helv. Chim. Acta* 1980, **63**, 1434.
39. Beckwith, A.L.J.; Moad, G. *J. Chem. Soc., Chem. Commun.* 1974, 472. Dewar, M.J.S.; Kirschner, S.; Kollmar, H.W. *J. Am. Chem. Soc.* 1974, **96**, 5240.

40. Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F.A. *Tetrahedron*, 1975, **31**, 1737.
41. Edge, D.J.; ; Kochi, J.K. *J. Am. Chem. Soc.* 1972, **94**, 7695; Krusic, P.J.; Kochi, J.K. *J. Am. Chem. Soc.* 1971, **93**, 846.
42. Beckwith, A.L.J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. II* 1979, 1535; Beckwith, A.L.J.; Blair, I.A.; Phillipou, G. *Tetrahedron Lett.* 1974, 2251.
43. Allinger, N.L.; Zalkow, V. *J. Org. Chem.* 1960, **25**, 701; Gream, G.E.; Serelis, A.K. *Aust. J. Chem.* 1978, **31**, 863.
44. Brown, H.C.; Bartholomay, H. Jr., Taylor, M.D. *J. Am. Chem. Soc.* 1944, **66**, 435.
45. Beckwith, A.L.J.; Gara, W.B. *J. Chem. Soc., Perkin Trans. II*, 1975, 795; Fumimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* 1972, **94**, 9205; Dewar, M.J.S.; Olivella, S. *J. Am. Chem. Soc.* 1978, **100**, 5290; Hoyland, J.R. *Theor. Chim. Acta* 1971, **22**, 229; Nagase, S.; Kern, C.W. *J. Am. Chem. Soc.* 1980, **102**, 4513.
46. Beckwith, A.L.J.; Gream, G.E.; Struble, D.L.; *Aust. J. Chem.* 1972, **25**, 1081; Struble, D.L.; Beckwith, A.L.J.; Gream, G.E. *Tetrahedron Lett.* 1968, 3701.
47. Beckwith, A.L.J.; Moad, G. *J. Chem. Soc., Perkin Trans. II*, 1975, 1726.
48. Beckwith, A.L.J.; Moad, G. *J. Chem. Soc. Chem. Commun.*, 1974, 472.
49. Beckwith, A.L.J.; Phillipou, G. *J. Chem. Soc.; Chem. Commun.* 1973, 280.
50. Wilt, J.W.; Mossie, S.N.; Dabeck, R.B. *J. Org. Chem.* 1970, **35**, 2803.
51. Beckwith, A.L.J.; Phillipou, G. *J. Chem. Soc., Chem. Commun.* 1971, 658.
52. Beckwith, A.L.J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* 1974, **96**, 1613.
53. Hoffmann, R.; Levin, C.C.; Moss, R.A. *J. Am. Chem. Soc.* 1973, **95**, 629.
54. Beckwith, A.L.J.; Lawrence, T.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* 1980, 484.
55. Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* 1980, 482.
56. Beckwith, A.L.J.; Phillipou, G.; Serelis, A.K. *Tetrahedron Lett.* 1981, 2811.
57. Wolff, S.; Agosta, W.C. *J. Chem. Res.* (S), 1981, 78.
58. Crandall, J.K.; Keyton, D.J. *Tetrahedron Lett.* 1969, 1653.
59. Ohnuki, T.; Yoshida, M.; Simamura, O. *Chem. Lett.* 1972, 797; Nagase, S.; Kern, C.W.

*J. Am. Chem. Soc.* 1979, **101**, 2544.

60. Ohnuki, T.; Yoshida, M.; Simamura, O.; Fukuyama, M. *Chem. Lett.* 1972, 999.
61. Ogibin, Y.N.; Troyanskii, E.I. *Akad. Nauk. SSSR, Ser. Khim.* 1975, 1461.
62. Griller, D.; Schmid, P.; Ingold, K.U. *Can. J. Chem.* 1979, **57**, 831.
63. Bakuzis, P.; Campos, O.O.S.; Bakuzis, M.L.F. *J. Org. Chem.* 1976, **41**, 3261.
64. Buchi, G.; Wuest, H. *J. Org. Chem.* 1979, **44**, 546.
65. Clive, D.L.J.; Beaulieu, P.L. *J. Chem. Soc., Chem. Commun.* 1983, 307.
66. Bachi, M.D.; Hoornaert, C. *Tetrahedron Lett.* 1981, 2689, 2693.
67. Bachi, M.D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* 1983, **48**, 1841.
68. Hart, D.J.; Tsai, Y.-M. *J. Am. Chem. Soc.* 1982, **104**, 1430.
69. Danishefsky, S.; Taniyama, E. *Tetrahedron Lett.*, 1983, 15.
70. Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* 1982, **104**, 5564.
71. Stork, G.; Mook, R. Jr.; Biller, S.A.; Rychnovsky, S.D. *J. Am. Chem. Soc.* 1983, **105**, 3741.
72. Nagashima, H.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *Tetrahedron Lett.* 1983, 2395.
73. Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.*, 1982, 2575.
74. Danishefsky, S.; Chackalamannil, S.; Uang, B.-J. *J. Org. Chem.* 1982, **47**, 2231.
75. Chuang, C.-P.; Hart, D.J. *J. Org. Chem.* 1983, **48**, 1782.
76. Stork, G.; Baine, N.J. *J. Am. Chem. Soc.* 1982, **104**, 2321.
77. Marinovic, N.N.; Ramanathan, H. *Tetrahedron Lett.* 1983, 1871.
78. Stork, G.; Mook, R. Jr. *J. Am. Chem. Soc.* 1983, **105**, 3720.
79. Okabe, M.; Tada, M. *Chem. Lett.* 1980, 831.
80. Okabe, M.; Abe, M.; Tada, M. *J. Org. Chem.* 1982, **47**, 1775.
81. Okabe, M.; Tada, M. *J. Org. Chem.* 1982, **47**, 5382.
82. Choi, J.-K.; Hart, D.J.; Tsai, Y.-M. *Tetrahedron Lett.* 1982, 4765.
83. Buchi, M.D.; Hoornaert, C. *Tetrahedron Lett.* 1982, 2505.
84. Stork, G.; Malhotra, S.; Thompson, H.; Uchibayashi, M. *J. Am. Chem. Soc.* 1965, **87**, 1148.
85. Pradhan, S.K.; Radhakrishan, T.V.; Subramanian, R. *J. Org. Chem.* 1976, **41**, 1943;

Pradhan, S.K.; Kadam, S.R.; Kolhe, J.N.; Radhakrishan, T.V.; Sohani, S.V.; Thaker, V.B. *J. Org. Chem.* 1981, **46**, 2622.

86. Koening, T.; Balle, T.; Snell, W. *J. Am. Chem. Soc.* 1975, **97**, 662; Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* 1972, **94**, 9205; Dewar, M.J.S.; Olivella, S. *J. Am. Chem. Soc.* 1978, **100**, 5290.

87. Strozier, R.W.; Caramella, P.; Hauk, K.N. *J. Am. Chem. Soc.* 1979, **101** 1340.

88. Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.* 1983, 2821.

89. Clive, D.L.J.; Anderson, P.C.; Moss, N.; Singh, A. *J. Org. Chem.* 1982, **47**, 1641; Clive, D.L.J.; Farina, V.; Beaulieu, P.L.B. *J. Org. Chem.* 1982, **47**, 2572.

90. Clive, D.L.J.; Chittattu, G.J.; Farina, V.; Kiel, W.A.; Menchen, S.M.; Russel, C.G.; Singh, A.; Wong, C.K.; Curtis, N.J. *J. Am. Chem. Soc.* 1980, **102**, 4438; Burke, S.D.; Fobare, W.F.; Armistead, D.M. *J. Org. Chem.* 1982, **47**, 3348.

91. Reich, H.J.; Trend, J.E. *Can. J. Chem.* 1975, **53**, 1922; Garratt, D.G.; Schmid, G.H.; Csizmadia, I.G. *J. Mol. Structure* 1974, **22**, 117; Schmid, G.H.; Garratt, D.G. *Chemica Scripta* 1975, 8A, 110.

92. Sharpless, K.B.; Lauer, R.F. *J.Org. Chem.* 1974, **39**, 429.

93. Clive, D.L.J. *J. Chem. Soc., Chem. Commun.* 1974, 100; Reich, H.J. *J. Org. Chem.* 1974, **39**, 428.

94. Denis, J.N.; Vicens, J.; Krief, A. *Tetrahedron Lett.* 1979, 2697.

95. Cambie, R.C.; Hayward, R.C.; Roberts, J.L.; Rutledge, P.S. *J. Chem. Soc., Perkin Trans. I* 1974, 1858.

96. Reich, H.J. *J. Org. Chem.* 1974, **39**, 428; Garratt, D.G.; Schmid, G.H. *Can. J. Chem.* 1974, **39**, 429.

97. Ikariya, T.; Osakada, K.; Yoshikawa, S. *Tetrahedron Lett.* 1978, 3749.

98. Das Gupta, T.K.; Felix, D.; Kempe, U.M.; Eschenmoser, A. *Helv. Chim. Acta* 1972, **55**, 2198; Itoh, A.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* 1979, 1783.

99. Petrzilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* 1973, **56**, 2950.

100. Fujita, T.; Suga, K.; Watanabe, S.; Yanagi, R.J. *Appl. Bioch. Tech.* 1977, **27**, 593.

101. Itoh, A.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* 1979, 1783; Herz, W.; Glick, L.A. *J. Org. Chem.* 1964, **29**, 613; Das Gupta, T.K.; Felix, D.; Kempe, U.M.; Eschenmoser, A. *Helv. Chim. Acta* 1972, **55**, 2198; Herz, W.; Glick, L.A. *J. Org. Chem.* 1963, **28**,

2970; Bertrand, M.; Dulcere, J.P.; Gil, G.; Grimaldi, J.; Sylvestre-Panthet, P. *Tetrahedron Lett.* 76, 3305.

102. Creger, P.L. *J. Org. Chem.* 1972, **37**, 1907.

103. The material is reported in Ref. 90 without spectroscopic data.

104. Meyers, A.I.; Mihelich, E.D.; Nolen, R.L. *J. Org. Chem.* 1974, **39** 2783.

105. Baldwin, J.E. *J. Chem. Soc. Chem. Comm.* 1976, 734.

106. Giese, B.; Lachein, S. *Angew. Chem. Int. Ed. Engl.* 1981, **20**, 967.

107. Smith, T.W.; Butter, C.B. *J. Org. Chem.* 1978, **43**, 6.

108. Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.* 1979, **8**, 171.

109. Dale, H. "Stereochemistry and Conformational Analysis," Verlag Chemie: New York, 1978, p. 217.

110. Barton, D.H.R.; Britten-Kelly, M.R.; Ferreira, D.J. *J. Chem. Soc., Perkin Trans. I* 1978, 1090; Denis, J.N.; Vicens, J.; Krief, A. *Tetrahedron Lett.* 1979, 2697; Garratt, D.G., Ryan, M.D.; Ujjainwalla, M. *Can. J. Chem.* 1979, **57**, 2145; Garratt, D.G. *Can. J. Chem.* 1979, **57**, 2180; Reich, H.J.; Renga, J.M. *J. Org. Chem.* 1975, **40**, 3313; Reich, H.J.; Renga, J.M.; Trend, J.E. *Tetrahedron Lett.* 1976, 2217; Clive, D.L.J.; Wong, C.K.; Kiel, W.A.; Menchen, S.M. *J. Chem. Soc. Chem. Commun.* 1978, 379; Clive, D.L.J.; Farina, V.; Singh, A.; Wong, C.K.; Kiel, W.A.; Menchen, S.M. *J. Org. Chem.* 1980, **45**, 2120; Wilson, S.R.; Sawicki, R.A. *J. Org. Chem.* 1979, **44**, 287.

111. Toshimitsu, A.; Toshiaki, A.; Owada, H.; Uemura, S.; Okano, M. *J. Org. Chem.* 1981, **46**, 4727.

112. Csizmadia, G.; Peterson, M.R.; Kozmutza, C.; Robb, M.A. "Chemistry of Acid Derivatives," Supplement B, Part 1, Patai, Wiley: New York, 1979, p. 27.

113. Barton, D.H.R.; McCombie, W. *J. Chem. Soc., Perkin Trans. I* 1975, 1574.

114. Robins, M.J.; Wilson, J.S. *J. Am. Chem. Soc.* 1981, **103**, 932.

115. Beckwith, A.L.J.; Phillipou, G.; Serelis, A.K. *Tetrahedron Lett.* 1981, 2811; Schimpf, R.; Heimbach, P. *Chem. Ber.* 1970, **103**, 2122.

116. Beslin, P.; Bloch, R.; Moinet, G.; Conia, J.-M. *Bull. Soc. Chim. Fr.* 1969, 508.

117. Stork, G.; Dowd, S.R. *J. Am. Chem. Soc.* 1963, **85** 2178.

118. Brown, C.A.; Yamashita, A. *J. Am. Chem. Soc.* 1975, **97**, 891.

119. Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* 1972, 3769.

120. *cf.* Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* 1983, 391.

121. *cf.* Stork, G.; Bizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* 1963, **85**, 207.

122. Pirkle, W.H.; Adams, P.E. *J. Org. Chem.* 1980, **45**, 4111.

123. Larock, R.C.; Oertle, K.; Potter, G.F. *J. Am. Chem. Soc.* 1980, **102**, 190.

124. Whitesell, J.K.; Matthews, R.S. *J. Org. Chem.* 1977, **42**, 3878.

125. Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* 1972, 1287.

126. Fieser and Fieser, "Reagents for Organic Synthesis, " Wiley, New York, 1969, Vol. 2, p. 409.

127. "Beilsteins Handbuch der Organischen Chemie, " Springer-Verlag Berlin EII, **2**, 392.

128. Kuivila, H.G.; Beumel, O. F. Jr. *J. Am. Chem. Soc.*, 1961, **83**, 1246.

129. Bogavac, M.; Arsenijevic, L.; Arsenijevic, V. *Bull. Soc. chim. Fr.* 1980, 145.

130. Bloomfield, J.J.; Lee, S.L. *J. Org. Chem.* 1967, **32**, 3919.

131. Rabjohn, N. "Organic Syntheses, " Wiley: New York, 1965, Collective Vol. IV, p. 630.

132. Lynn, J.W.; Roberts, R.L.; Kilsheimer, J.R. *J. Org. Chem.* 1961, **26**, 4300.

133. Barieux, J.-J.; Gore, J. *Bull. Soc. chim. Fr.* 1971, 1649.

134. Layer, R.W. *Chem. Rev.* 1963, **63**, 489.

135. Harding, K.E.; Ligon, R.C.; Tseng, C.-Y.; Wu, T.-C. *J. Org. Chem.* 1973, **38**, 3478; Mahajan, J.R.; DeAravjo, H.C. *Synthesis* 1981, 49; Pennanen, S. *Acta Chem. Scand. Ser. B* 1980, **B34**, 261.

136. Julia, M.; Fourneron, J.-D. *J. Chem. Res. (S)* 1978, 466; Julia, M.; Colomer Gazquez, E. *Bull. Soc. Chim. Fr.* 1972, 4148.

137. Ried, W.; Beck, B.M. *Annalen* 1961, **646**, 96.

138. LaForge, F.B.; Green, N.; Gersdorff, W.A. *J. Am. Chem. Soc.* 1948, **70**, 3709.

139. Barluenga, J.; Yus, M.; Bernad, P. *J. Chem. Soc. Chem. Commun.* 1978, 847.

140. Horning, E.C. "Organic Syntheses, " Wiley: New York, 1955, Collective Vol. III, p. 188.

141. Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. *J. Chem. Soc.* 1959, 112.

142. Johnson, W.L. *Chem. Abstr.* 1949, **43**, 678i; ApSimon, J.; Seguin, R. *Synth. Commun.* 1980, **10**, 897.

143. Ferdinandi, E.S.; Just, G. *Can. J. Chem.* 1971, **49**, 1070.

144. Vedejs, E.; Arnost, M.J.; Hagen, J.P. *J. Org. Chem.* 1979, **44**, 3230.

145. Svirskaya, P.I.; Leznoff, C.C.; Weatherston, J.; Laing, J.E. *J. Chem. Eng. Data* 1979, **24**, 152.

146. Rabjohn, N. "Organic Syntheses, " Wiley: New York, 1965, Collective Vol. IV, p. 117.

147. Pond, D.M.; Cargill, R.L. *J. Org. Chem.* 1967, **32**, 4064.

148. Heilbron, I.M.; Heslop, R.N.; Irving, F.; Wilson, J.S. *J. Chem. Soc.* 1931, 1336.

149. Mayer, R.; Wenschuk, G.; Topelmann, W. *Chem. Ber.* 1958, **91**, 1616.

150. LaForgue, F.; Green, N.; Gersdorff, N. *J. Am. Chem. Soc.* 1948, **70**, 3707; Derocque, J.; Beisswenger, U.; Hanach, M. *Tetrahedron Lett.* 1969, 2149.

151. Glennon, R.A.; Salley, J.J. Jr.; Steinsland, O.S.; Nelson, S. *J. Med. Chem.* 1981, **24**, 678.

152. Eglinton, G.; Whiting, M. *J. Chem. Soc.* 1950, 3650.

153. Bhanu, S.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. I*, 1979, 1218.

154. Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J.G.; Larue, M.; Young, R.N.; Masson, P.; Holme, G. *Tetrahedron Lett.* 1980, **21**, 1485.

155. Stowell, J.C.; Keith, D.R. *Synthesis* 1979, 132.

156. Frater, G. *Helv. Chim. Acta* 1980, 1383.

157. Conrow, R.E.; Marshall, J.A. *Synth. Commun.* 1981, **11**, 419. Hatch, L.F.; Perry, R.H. Jr. *J. Am. Chem. Soc.* 1955, **77**, 1136.

158. House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* 1969, **34**, 2324.

159. Nienhouse, E.J.; Irwin, R.M.; Finni, G.R. *J. Am. Chem. Soc.* 1967, **89**, 4557.

160. Dufey, P. *Bull. Soc. Chim. Fr.* 1968, 4653.

161. Eglinton, G.; Whiting, M.C. *J. Chem. Soc.* 1950, 3650.

162. Rabjohn, N. "Organic Syntheses, " Wiley: New York, 1965, Collective Vol. IV, p. 755.

163. Mandville, G.; Leyendecker, F.; Conia, J.-M. *Bull. Soc. Chim. Fr.* 1973, 963.

164. Hudec, J.; Kirk, D.N. *Tetrahedron* 1976, **32** 2475; Meyers, A.I.; Ford, M.E. *Tetrahedron Lett.* 1975, 2861.

165. Lewis, P.H.; Middleton, S.; Rosser, M.J.; Stock, L.E. *Aust. J. Chem.* 1979, **32**, 1123.

166. Dupuy, C.; Surzur, J.-M. *Bull. Soc. Chim. Fr.* 1980, 374; Newman, N.; Wobiz, J. *J. Am. Chem. Soc.* 1949, **71**, 1292.

167. Truce, W.E.; Klinger, T.C. *J. Org. Chem.* 1970, **35**, 1834.

168. Friedrich, K.; Henning, H.G. *Chem. Ber.* 1959, **92**, 2756.

169. Hutchins, R.O.; Natale, N.R. *J. Org. Chem.* 1978, **43**, 2299.

170. Hutchins, R.O.; Kacher, M.; Rua, L. *J. Org. Chem.* 1975, **40**, 923.

171. Kuehne, M.E. *J. Am. Chem. Soc.* 1959, **81**, 5400.

172. Trost, B.M.; Bogdanowicz, M.J. *J. Am. Chem. Soc.* 1973, **95**, 5311.

173. *cf.* White, W.A.; Weigarten, H. *J. Org. Chem.* 1967, **32**, 213.

174. Brown, H.C.; Schlesinger, H.I.; Sheft, I.; Riter, D.M. *J. Am. Chem. Soc.* 1953, **75**, 192.

175. Brenner, W.; Heimbach, P.; Ploner, K.J.; Thoemel, F. *Justus Liebigs Ann. Chem.* 1973, **11**, 1882.

176. Klunk, W.E.; McKeon, A.C.; Covey, D.F.; Ferrendelli, J.A. *Science* 1982, **217**, 1040.

# ADDENDA

**1-Tridecen-6-ol 79** (p. **174**): exact mass, m/e 99.0808 (calcd for $C_6H_{11}O$, $M^{+}-C_7H_{15}$, m/e 99.0810).

**Authentic *cis*-decahydro-1-methylene-naphthalene 144a** (p. **194**): exact mass m/e 150.1388 (calcd for $C_{11}H_{18}$, m/e 150.1408).

**Authentic *trans*-decahydro-(*E*)- and (*Z*)-1-benzylidene-naphthalenes 151cd** (p. **198**): exact mass, m/e 226.1723 (calcd for $C_{17}H_{22}$, m/e 226.1721).